KETENIMINIUM YLIDS AND FLUOROSULFONATE SALTS: PRECURSORS TO NOVEL HETEROCYCLIC SYSTEMS

By

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to my parents

Benjamin Sylvester

and

Stephania Anna Kuta

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Abstract of Dissertation Presented to the Graduate Council
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KETENIMINIUM YLIDS AND FLUOROSULFONATE SALTS:
PRECURSORS TO NOVEL HETEROCYCLIC SYSTEMS

By

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December, 1976

Chairman: James A. Deyrup
Major Department: Chemistry

A new route to the theoretically interesting alkylidene aziridine series was explored. Di-t-butylketene-N-ethylimine was methylated with methylfluorosulfonate to give the respective keteniminium fluorosulfonate salt in high yield. Deprotonation of this salt with sodium bis-(trimethylsilyl)amide in benzene failed to effect the anticipated electrocyclic ring closure to its alkylidene aziridine viz a keteniminium ylid. Instead, dimerization to N,N' diethyl-2,5-bis(2,2,4,4-tetramethyl-3-pentylidene)piperazine occurred, presumably by a $\pi_4 + \pi_4$ cyclization of the 1,3-dipolar intermediate. Experimental evidence for the intervention of a keteniminium ylid is given. Spectroscopic and mechanistic interpretations are also discussed.

The alkylation of ketenimines not bearing sterically protecting t-butyl groups on the ketene terminus gave different results. On treatment with methyl fluorosulfonate, N-aryl ketenimines produced quinazolicium salts and/or perhydro-s-triazines, depending upon the

one of the substituents carried on the ketene terminus. N-Alkyl ketenimines gave only 2-imidoazetidinium fluorosulfonate salts. Spectroscopic data and mechanistic interpretations are discussed.

The behavior of α-chloroenamines under deprotonation is described. In most cases, addition or dealkylation products were obtained. Mechanisms consistent with these transformations are described.

A system theoretically tailored to undergo a rare 3+1 cycloaddition was investigated. The addition of t-butylisonitrile to ethyl trans-1,3-diphenylaziridinecarboxylate was effected in solution with carbon tetrachloride. The expected 3+1 cycloaddition product was not observed, however, phenyl-(N-phenyl-N-carbethoxymethyl)aminoketone-N'-t-butylimine was obtained in excellent yield. Trace acid impurities present in carbon tetrachloride were implicated in the high conversion to the aminoketenimine. Mechanistic details are discussed.

CHAPTER I

KETENIMINIUM YLIDS:

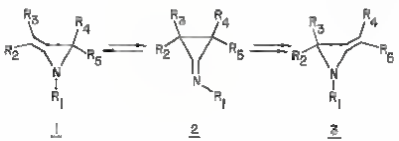
SYNTHESIS AND DEPROTONATION OF

Di-t-BUTYLKETENE-N-METHYL-N-ETHYLIMINIUM

FLUOROSULFONATE

Introduction

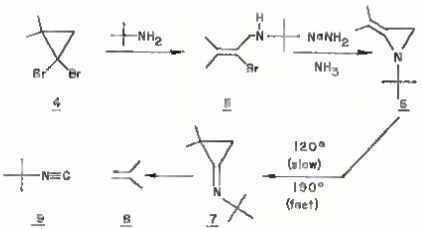
Alkylidene aziridines of the general structure 1 and their valence bond isomers 2 and 3 are relatively obscure compounds. They have only recently attracted the attention of synthetic chemists



(1)

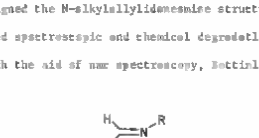
because of their analogy to the methylene cyclopropane system, and hence their potential for molecular reorganization.[1-4] Indeed, Quast and Ricsler[2] observed the thermal rearrangement of the isopropylidene aziridine 6 to the imine cyclopropane 7 as illustrated in Scheme 1.

SCHEME I



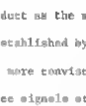
At higher temperatures or on prolonged heating, this imine cyclopropane 7 decomposes quantitatively to the olefin 8 and t-butylisonitrile 9. On the basis of nmr kinetic studies, the activation energy for the 6 to 7 isomerization was estimated to be approximately 34 kcal/mole.

Methylene aziridines were first prepared by Fallard and Purcell[5] by treating selected N-(2-bromoallyl)alkylamines with sodium amide in liquid ammonia according to equation (2). The product, however, was



(2)

erroneously assigned the N-alkylallylidenemeimine structure 12 on the basis of infrared spectroscopic and chemical degradation data. Several years later, with the aid of nmr spectroscopy, Bottini and Roberts[6]

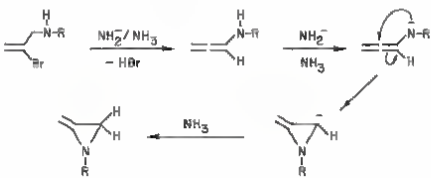


correctly identified the product as the methylene aziridine 11.

The structure 11 was established by its strong infrared absorption band near 1770 cm^{-1},[6,7] and, more convincingly, by its nmr spectrum which showed singlet resonance signals at δ 4.78 and 1.55 corresponding to the exocyclic vinylic and cyclic methylene protons respectively. Mechanistic studies performed later by Bottini and Olsen[8] using tritiated ammonia indicated that isotopic labelling occurred at the

ring carbon of the methylene aziridine. Since these protons failed to undergo exchange with solvent under control conditions, an elimination addition mechanism of the type depicted in Scheme ii was proposed

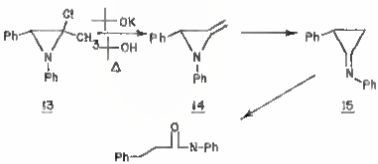
SCHEME II



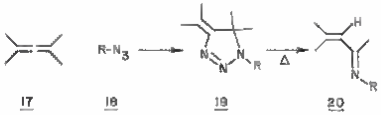
Nearly a decade later, Deyrup and Greenwald[9] reported an unusual rearrangement of aziridine 13 When refluxed in t-butanol with an excess of potassium t-butoxide, 13 was converted to a product identified as hydrocinnamanilide 16. It was suggested that the rearrangement was initiated by dehydrochlorination of the aziridine 13 to give the methylene aziridine 14 which subsequently isomerized to the imino cyclopropane 15 under the experimental conditions. A relatively straightforward mechanism was proposed by the transformation of 15 to the amide 16.[9,10]

Kleiholder and Shechter[11] attempted to provide a direct synthesis of substituted alkenimines by the addition of nitrenes via the thermal or photolytic decomposition of electronegatively substituted azides to alkenes. In most cases, 1,3-dipolar addition to the olefinic linkage of the alkene took place with the formation of 1,2,3-triazolines 19 Thermal decomposition of these triazolines, which in other systems were known to produce aziridines and imines,[12] gave only α,β-unsaturated

SCHEME III



Schiff bases 20. In one system, thermolysis of ethyl azidoformate 21 in refluxing tetramethylallene 17 produced in addition to triazoline 22, a compound which had spectral properties consistent with oxazoline 23.[13] The origin of 12 was not unequivocally established. Two possible modes



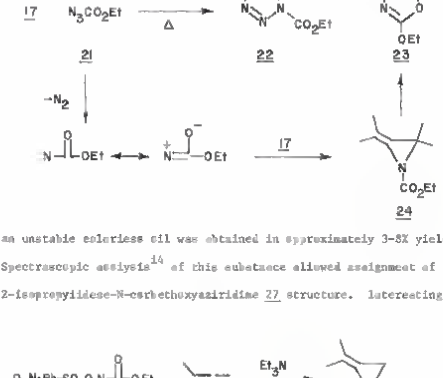
(3)

of attack by the nitrene across the allene were suggested: a 1,3 dipolar cycloaddition of carbethoxy nitrene to the allene, or a 2+1 addition to give aziridine 24 which then rearranged via a 1,5 sigmatropic isomerization under the experimental conditions. In no instance was direct evidence for an alkylidene aziridine given.

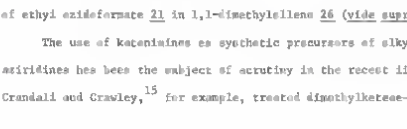
More recently, Bingham and Gilbert[3] have reinvestigated the addition of ethyl azidoformate 21 to substituted allenes. Base-catalyzed β-elimination of N-(p-nitrobenzenesulfonoxy)urethane was used as a source of carbethoxynitrene. Upon treatment of a dilute methylene

chloride solution of 1,1 dimethylsilene 26 with carbethoxy nitrene,

SCHEME IV



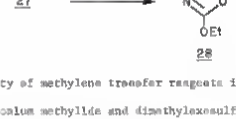
an unstable colorless oil was obtained in approximately 3-8% yield Spectroscopic analysis[14] of this substance allowed assignment of the 2-isopropylidene-N-carbethoxyaziridine 27 structure. Interestingly,



(4)

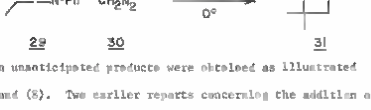
thermolysis at 130° of a dilute solution of 27 in carbon tetrachloride produced the oxazoline 28. This was identical to the material obtained by Bleiholder and Shechter[11] for the adduct formed from the photolysis of ethyl azidoformate 21 in 1,1-dimethylsilene 26 (vide supra).

The use of ketenimines as synthetic precursors of alkylidene aziridines has been the subject of scrutiny in the recent literature Crandall and Crawley,[15] for example, treated dimethylketene-N-phenylimine



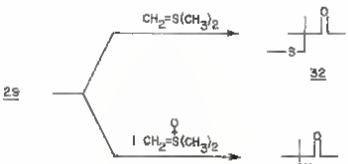
(5)

with a variety of methylene transfer reagents including diazomethane, dimethylsulfonium methylide and dimethylsoxsulfonium methylide. Addition of diazomethane to ketenimine 29 proceeded sluggishly, and afforded cyclobutanone anil 31 in low yield as the only identifiable product. Treatment of 29 with sulfur ylids proceeded readily, but



(6)

again unanticipated products were obtained as illustrated in equations (7) and (8). Two earlier reports concerning the addition of carbenes



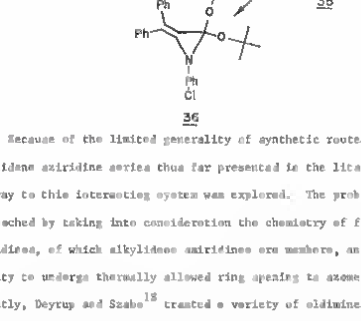
(7)

(8)

to ketenimines showed addition occurring across the carbon-nitrogen bond rather than the carbon-carbon bond as observed by Crandall and Crowley.[15] Barker and Gardner[16] reported that diazomethane added

smoothly to diphenylketene-N-(p-bromophenyl)imine to yield a 1,2,3-triazole. Ichimura and Ohta,[17] on the other hand, determined that addition of dichlorocarbene to diphenylketene-N-(p-chlorophenyl)imine 34 did not give the expected product 35. Instead, a compound was isolated with elemental composition and spectroscopic properties in agreement with the benzhydrylidene aziridine 36.

SCHEME V

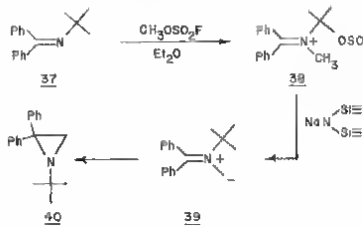


Because of the limited generality of synthetic routes to the alkylidene aziridine series thus far presented in the literature, a new pathway to this interesting system was explored. The problem was approached by taking into consideration the chemistry of functionalized aziridines, of which alkylidene aziridines are members, and their ability to undergo thermally allowed ring opening to azomethine ylids. Recently, Deyrup and Szabo[18] treated a variety of aldimines and ketimines with methyl fluorosulfonate and obtained respective fluorosulfonate salts in high yields. In one case, deprotonation with a nonnucleophilic strong base produced aziridine 40 in quantitative yield,

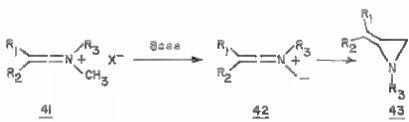
presumably *via* the azomethine ylid 39.

This research was directed toward the generation of a keteniminium ylid of the general structure 42 *via* alkylated keteniminium salts 41

SCHEME VI



with the intent of observing cyclization to the corresponding alkylidene aziridine 43. This approach seemed particularly promising not only



(9)

because of its mimicry of azomethine ylids, but also due to its striking resemblance to the mechanism (Scheme II) proposed by Bottini and Olsen[8] for the cyclization of N-(2-bromoallyl)alkylamines to methylene aziridines.

Although isolable keteniminium salts are not known, solutions of fluoroborate salts from the treatment of α-chloroenamines with silver fluoroborate have been prepared.[15] These solutions proved to be

extremely responsive to electrophilic substitution on activated aromatic systems,[19] 2+2 cycloadditions with olefins[20,21] and Schiff bases,[22] and in general exceptionally hygroscopic and vulnerable toward attack by nucleophilic reagents.[23] The high reactivity, or conversely the low stability of these keteniminium fluoroborate salts is explicable in part by the size or bulk carried by its substituents. It is known, for example, that whereas triaryl ketenimines are comparatively stable yellow oils or low melting solids, most trialkyl ketenimines are thermally unstable with respect to polymerization, and tend to hydrolyze readily to thioic amides.[24] All of the keteniminium fluoroborate salts presently known are tetraalkyl substituted with groups no larger than ethyl. As a result, the small volume occupied by these substituents offers virtually no resistance to nucleophiles approaching the highly energetic sp-hybridized central carbon of the keteniminium salt. These salts for obvious reasons show no tendency to polymerize, but otherwise are potent electrophiles.

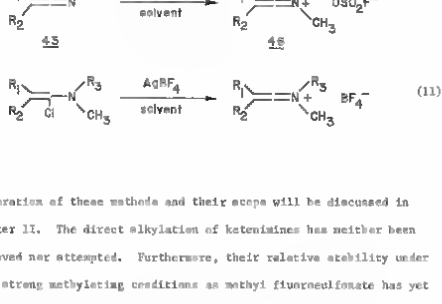
The selection of a suitable keteniminium salt prior to its synthesis was, therefore, subject to certain structural constraints. First, the substituents had to be large enough to stabilize its formation, and subsequently its conversion to a three membered ring.[25] Substituent effects of this nature were implicated in the remarkable stability of di-t-butylketene 44.[26,27] Unlike most aliphatic ketenes

44

which dimerize rapidly and readily attept nucleophilic reagents,[28] ketene 44 was easily distilled as a stable monomer and showed a marked

resistance toward attack by nucleophiles.[26] Secondly, these substituents must necessarily be inert to the strongly basic conditions[18] needed to achieve deprotonation to the corresponding ylid 42. Thirdly, the counterion, X^-, should be reasonably bulky and nonnucleophilic in order to discourage attack at the iminium carbon and/or otherwise interfere with the stability or chemical conversion of 41 to 43. Scheme VII illustrates the two proposed pathways to be investigated in this work. The first (10) involves the direct alkylation of ketenimines 45. Ketenimines in general can be synthesized from secondary amide precursors by a variety of straightforward methods.[29-33]

SCHEME VII



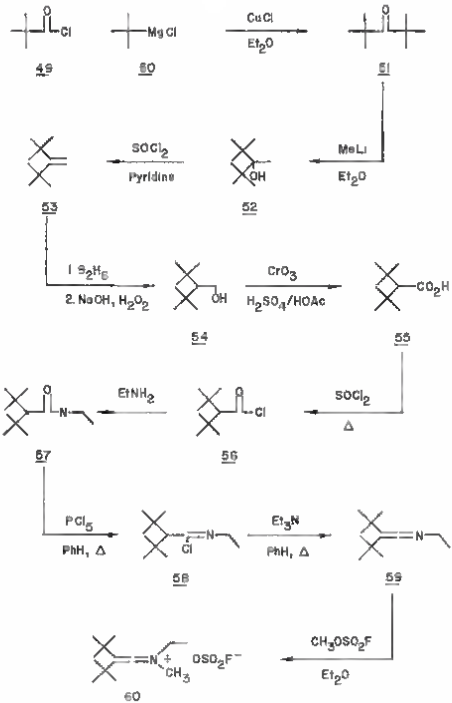
Elaboration of these methods and their scope will be discussed in Chapter II. The direct alkylation of ketenimines has neither been achieved nor attempted. Furthermore, their relative stability under such strong methylating conditions as methyl fluorosulfonate has yet to be tested.

The treatment of α-chloroenamines 47 (10) with silver fluoroborate (vide supra) and their behavior under deprotonation conditions will be discussed in a later chapter.

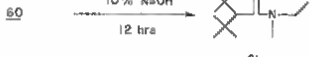
Results

The sterically protected di-t-butylketene-N-ethylimine 59 was synthesized via its precursors 49 through 58 as depicted in Scheme VIII. The sequence 49 through 56 was carried out according to known literature procedures[26,34] while the aminolysis 57 was accomplished as a partial objective in this research. The conversion of acid chloride 56 to the ethylamide 57 took place smoothly (82%) in liquid ethylamine despite the reported[26] vigorous conditions needed to transform 56 to its primary amide with sodium amide in liquid ammonia. Amide 57 was treated with one equivalent of phosphorus pentachloride under the mild conditions of refluxing benzene. The imidoyl chloride 58 was not isolated. Instead, it was dehydrochlorinated directly with triethylamine to a mixture (ca. 75:25) which contained ketenimine 59 and a substance believed to be di-t-butylacetonitrile.[35] Ketenimine 59 exhibited a parent ion at m/e 181.1827 (calcd for $C_{12}H_{23}N$: 181.1830) in the mass spectrum. The appropriate signals and multiplicities were observed in its nmr spectrum as well as a strong and very characteristic infrared maximum at 1998 cm^{-1} associated with the heterocumulene functionality, C=C=N.[36,37] Attempts to isolate an analytical sample of 59 completely free of nitrile either by conventional distillation techniques or by column chromatography resulted in only slight purification. Nevertheless, the alkylation was performed by syringing a twofold excess of methyl fluorosulfonate[39] into a stirred ethereal solution containing ketenimine 59. Methylation occurred rapidly and selectively at the ketenimine nitrogen, resulting in an almost immediate precipitation of the keteniminium fluorosulfonate salt 60 as a white flocculent solid. This material was determined by spectroscopic

SCHEME VIII


49
50
CuCl
Et_2O
51
MeLi
Et_2O
52
$SOCl_2$
Pyridine
53
1. S_2H_6
2. NaOH, H_2O_2
54
CrO_3
H_2SO_4/HOAc
55
$SOCl_2$
Δ
56
$EtNH_2$
57
PCl_5
PhH, Δ
58
Et_3N
PhH, Δ
59
CH_3OSO_2F
Et_2O
60

analysis to be completely void of nitrile and/or alkylated nitrile by-products. Ketoniminium salt 60 proved to be remarkably stable (mp 224-228° with decomposition) considering its activated environment and the known chemistry of other heterocumulenes.[18,24,38] It has a high degree of solubility in polar solvents such as chloroform, ethanol, or water, and can be recrystallized from methylene chloride/ether. Surprisingly, it is resistant under neutral hydrolysis conditions to the point where it can be recovered unchanged after stirring in aqueous solution at room temperature for two hours or more! The infrared spectrum of 60 shows a band of medium intensity at 2000 cm^{-1} for the ketenimine functionality. This band seems to be at somewhat lower frequency than expected for a ketenimine with a positively charged heteroatom. Schiff bases, for example, show appreciable infrared shifts to higher frequency upon protonation or alkylation.[36] Also, the higher frequency of isocyanates[36] (ca. 2275 cm^{-1}) and ketenes[37] (ca. 2150 cm^{-1}) compared with that of 60 tend to make the band at 2000 cm^{-1} appear curiously low. Present in the nmr spectrum is a low field t-butyl signal at δ 1.39 and a deshielded methyl singlet at δ 3.90, as well as the required ethyl pattern at δ 1.48 (triplet) and δ 4.11 (quartet). As further structural proof, 60 was hydrolyzed in aqueous base to its tertiary amide 61 according to equation (12).

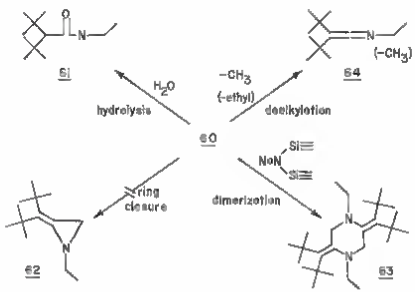


(12)

The structure of this amide was established by high resolution mass spectrometry with a parent ion at m/e 213.2092 (calcd for $C_{13}H_{27}NO$ 213.2092), and by its infrared and nmr characteristics.

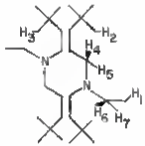
The deprotonation of 60 was performed in benzene using sodium bis(trimethylsilyl)amide as a sterically hindered, nonnucleophilic strong base.[18] Stirring a slurry of 60 in benzene with excess base for 24 hours produced the piperazine dimer 63 in 52% yield rather than the intended aziridine 62. The dimeric structure of 63 was confirmed by its high resolution mass spectrum with a parent ion at m/e 390.3977 (calcd for $C_{26}H_{50}N_2$ 390.3973).

SCHEME IX



The geminal nonequivalent endocyclic methylene protons (H_4, H_5) of piperazine 63 appeared as an AB pattern in the nmr with coupling constants and chemical shift data shown in Table I.

Table 1
100 MHz Proton Spectrum of
Piperazine Dimer 63



63

Proton	δ	Multiplicity	J
H_1	1.07	triplet	$J_{1,6(7)}$=7 Hz
H_2	1.30	singlet	
H_3	1.33	singlet	
H_4	2.60	doublet	$J_{4,5}$=10 Hz
H_5	3.35	doublet	$J_{5,4}$=10 Hz
H_6	3.02	doublet of quartets	$J_{6,7}$=12 Hz, $J_{6,1}$=7 Hz
H_7	2.72	doublet of quartets	$J_{7,6}$=12 Hz, $J_{7,1}$=7 Hz

The exocyclic methylene protons (H_6, H_7) displayed an interesting quartet of quartets pattern which collapsed to a simple AB system upon spin decoupling of the methyl protons (H_1). The geminal nonequivalence of these protons (H_6, H_7) can be attributed to restricted rotation of the N-ethyl groups of 63.[41] Inspection of molecular models clearly shows a considerable degree of steric interaction between the N-ethyl substituent and its neighboring t-butyl group. Also, the t-butyl

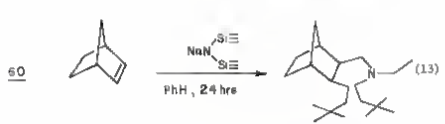
resonance occurring 13.5 Hz (δ 0.124 ppm) downfield relative to the t-butyl signal at δ 1.30 could conceivably be the result of steric compression which is known to cause paramagnetic shifts of this magnitude.[42]

Minor components appearing in the deprotonation product mixture showed infrared absorption bands at rather weak intensity at ca. 2000 and 1640 cm^{-1}. These were interpreted as arising from dealkylation and hydrolysis of the ketenimonium salt 60 during the prolonged reaction times. Dealkylation has been noted by Deyrup and Szabo[18] to be an annoying side reaction, but in general could not be entirely eliminated. Partial hydrolysis of 60 was expected to occur due to trace amounts of moisture in the solvent and/or hydroxide contaminants present in the silylamide base.

Attempts to encourage ring closure by performing the deprotonation in refluxing benzene again produced piperazine 63 and in somewhat higher yield (59%). Deprotonation under the homogeneous conditions of hexamethylphosphoramide (HMPA) resulted in a drastic decrease in dimerization (21%), but only at the expense of hydrolysis to the amide 61 (52%). Further attempts to effect cyclization were abandoned, and attention was focused on the identity of the supposed "1,3-dipolar" precursor of 63.

Stereospecific additions to 1,3-dipolarophiles have been of profound importance in establishing the intermediacy of azomethine ylide during the course of aziridine isomerizations.[43-45] These trapping experiments are now recognized as convincing evidence for the intervention of other 1,3 dipoles as well. Unfortunately, capture of *in situ* generated 1,3-dipoles by conventional trapping agents was

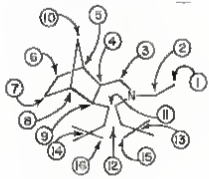
subject to major experimental problems. Most desirable dipolarophiles[18] would hardly withstand the severity of the strongly basic conditions required for dipole formation. Norbornene 65, however, was found to be completely inert to the silylamide base under the deprotonation conditions. Treatment of 60 with sodium bis(trimethylsilyl)amide in the presence of a tenfold excess of norbornene 65 formed the 1:1 adduct 66. Attempted



purification by short path distillation resulted in some sample decomposition with no substantial improvement in product quality. Spectroscopic analysis of adduct 66 before distillation revealed a parent ion at m/e 289 2761 (calcd for $C_{20}H_{35}N$ 289 2769). Complete analysis of the mass spectrum suggested the presence of at least one other component. The identity and relative percentage of this by-product(s), however, was not determined (vide infra). Nmr analysis showed the expected nonequivalent t-butyl signals at δ 1.35 and 1.50, a methyl triplet at δ 1.00 as well as unresolved methylene and norbornyl multiplets in the range δ 1.0-3.0. ^{13}C nmr (Table II) proved to be helpful in establishing the presence of the olefinic linkage carrying the t-butyl groups. These appeared as singlets at δ 141.4 and δ 124.8 downfield from internal TMS and are in agreement with typical shifts for sp^2 hybridized carbons. The assignments made in Table II were based on the multiplicities extracted from single frequency off-resonance decoupling data together with typical chemical shift values for model norbornyl and pyrrolidine derivatives.[47] Some of these assignments may

Table II

^{13}C Chemical Shift Data for 66



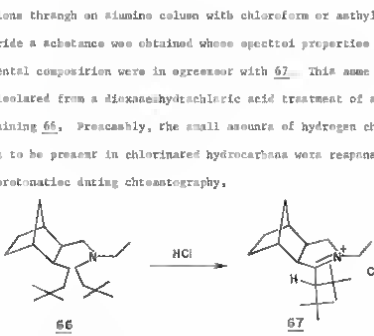
66

δ*	Multiplicity	Assignment
16.0	quartet	1
26.2	triplet	6
31.1	quartet	16
31.6	triplet	7
32.6	quartet	15
33.6	singlet	14
36.0	singlet	13
36.7	doublet	5
41.1	doublet	8
41.8	triplet	10
44.3	triplet	2
51.1	doublet	4
54.6	doublet	9
57.4	triplet	3
124.8	singlet	12
141.6	singlet	11

*chemical shifts are reported downfield from internal TMS with deuterochloroform as a solvent

be in error due to close differences in chemical shifts, but, for the most part, the spectrum fits well for the proposed structure 66. The infrared spectrum contained a weak band at ca. 1625 cm^{-1} characteristic of the enamine functionality.[36]

Interestingly, adduct 66 was unexpectedly derivatized during an attempted purification via column chromatography. After several elutions through an alumina column with chloroform or methylene chloride a substance was obtained whose spectral properties and elemental composition were in agreement with 67. This same product was isolated from a dioxane-hydrochloric acid treatment of a distillate containing 66. Presumably, the small amounts of hydrogen chloride known to be present in chlorinated hydrocarbons were responsible for the protonation during chromatography.

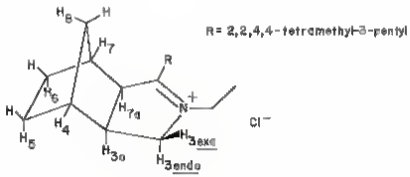


(14)

The nmr spectrum of this derivative was much more informative than that of 66. The positively charged nitrogen greatly deshielded the adjacent pair of methylene protons which separating the $H_{3\alpha}$ and $H_{7\alpha}$ endo protons by approximately 0.75 ppm. Table III provides chemical shift values and a partial list of coupling constants for 67. The exo configuration of adduct 67 was established by the magnitude of the $H_{3\alpha}$-$H_{7\alpha}$ (endo, endo) proton coupling constant (8.0 Hz), and the ample literature precedent for the preferred exo addition of 1,3-dipoles to norbornene.[44,46] In general, the endo-endo coupling constant by itself

Table III

NMR Chemical Shift and Coupling Constant Data for 67



67

Proton	δ	J	Calcd (Hz)	Obsd (Hz)
H_5,H_6,H_8	1.33–1.85			
H_7	2.48	$J_{7,7a}+J_{7,4}+J_{7,6endo}+J_{7,6exo}$	6.7(+2.7)[48,49]	6.5[48]
H_{3a}	2.76	$J_{3a,7a}$	8.0[46]	8.0
		$J_{3a,3endo}$	9.5[46]	10.5
H_4	ca. 2.88			
H_{7a}	3.38	$J_{7a,3a}$	8.0[46]	8.0
		$J_{7a,3exo}+J_{7a,7}+J_{7a,8}$	5.7(±1.5)[48,49]	5.5[48]
H_{3exo}	ca. 3.83–4.5			
H_{3endo}	4.83	$J_{3endo,3exo}$	12–15[49]	15.0

is not conclusive evidence for an exo adduct assignment. A more convincing argument can be made by comparing both the H_{3a}-H_{7a} (endo,endo) coupling (6-8 Hz) and the bridgehead-endo coupling (0-2 Hz). Unfortunately, long range "W" coupling precluded accurate evaluation of these J values. An estimation of the total coupling (vicinal and "W") was made by evaluating the width at half height for the H_7 (bridgehead) and H_{7a} (endo) resonances respectively. These values were compared with calculated values (Table iii) using the empirical relationship and average values

$$\Delta\nu_{1/2} = J_{1,2} + J_{1,3} + \cdots$$

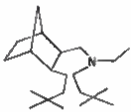
from suitable model compounds. The calculated values for an exo adduct were shown to agree quite well with those observed for 67.

An inflected band at 1620 cm^{-1}[46,50] and a ^{13}C singlet at δ 195[47] strongly suggest the presence of the imidium functionality ($C{=}N^{+}$). High resolution mass spectrometry failed to show a parent ion at m/e 326 for the hydrochloride salt 67. Instead, a pseudo parent ion at m/e 289.2763 (calcd for P^{+}-HCl 289.2769) was observed. The conspicuous loss of HX from salts of this type has been noted to occur in other analogous systems in this work (Chapter III). These spectra show fragmentation patterns identical to those of their chemically deprotonated derivatives. In one case, it was established that loss of HX occurred in the probe of the mass spectrometer prior to its entry into the ionization chamber.[51] A tabulation of the initial major fragmentations of 67 is given in Table IV. These are compared with m/e values obtained from the mass spectral analysis of freshly prepared 66. It appears that dehydrochlorination of 67 is occurring to give 66 which then produces the observed fragmentations.

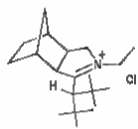
The iminium bond of the hydrochloride salt 67 was surprisingly

Table IV

A Partial Tabulation of Mass Spectral Fragmentations Obtained from 66 and 67



66

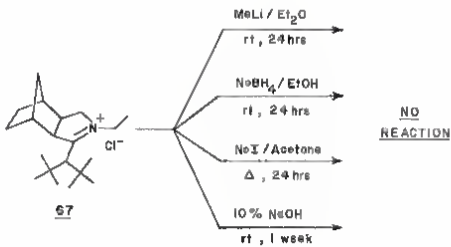


67

m/e	Relative Intensity (%)	
	66	67
289 (P^{+})	1.8	2.0
274	2.6	3.3
233	13.5	13.4
232	19.6	23.0
219	17.5	16.7
218	100.0	100.0

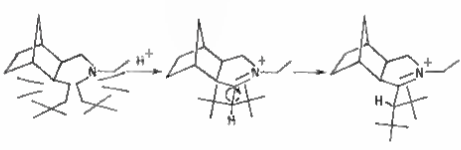
inert toward attack by a variety of reagents including methyl lithium (addition and/or deprotonation), sodium borohydride (reduction), sodium iodide (dealkylation), and aqueous sodium hydroxide (deprotonation and/or hydrolysis). The unusual preciivity of adduct 66 to scavenge HCl and the marked resistance of 67 toward deprotonation warrant further comment. Structural analysis of 66 via molecular models show that extreme crowding between the t-butyl groups and the norbornyl skeleton is

SCHEME X

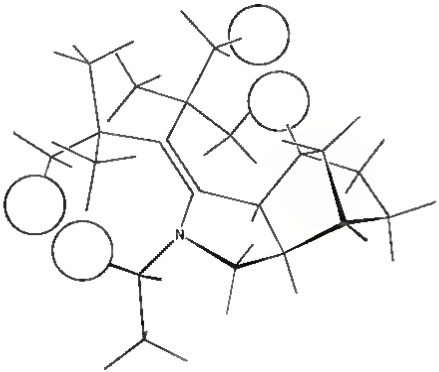


unavoidable (cf. figure 1). Substantial steric relief, though, is experienced on protonation when rotation of the carbon bearing the t-butyl groups assumes a thermodynamically more stable conformation (cf. figure 2) as illustrated in Scheme XI. The resistance of 67 to

SCHEME XI

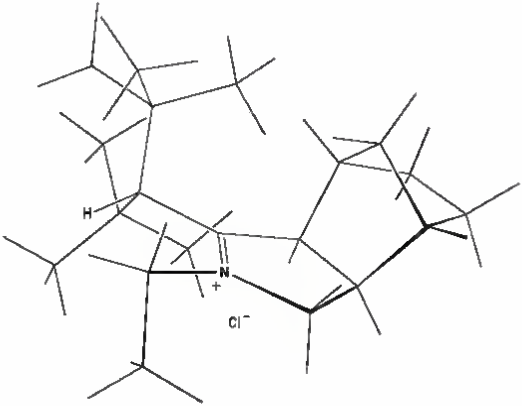


deprotonation should now be obvious: for proton abstraction to occur the carbon bearing the t-butyl groups must rotate into a sterically demanding conformation so that the proton to be removed assumes a periplanar arrangement with the p-orbital of the iminium bond. This



exo-N-Ethyl-1-(2,2,4,4-tetramethyl-3-pentylidene)perhydro-4,7-methanoisoindole (66).

Figure 1.

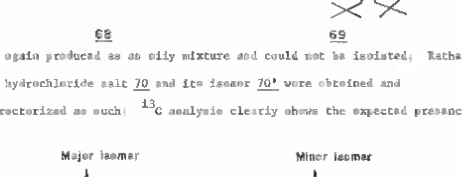


exo-N-Ethyl-1-(2,2,4,4-tetramethyl-3-pentyl)-3a,4,5,6,7,7a-hexahydro-4,7-methano-3H-isoindolinium chloride (67).

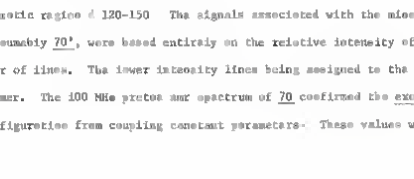
Figure 2

unfavorable feature results in its reluctance to respond under deprotonation conditions. The strong basicity of 1,8-bis(dimethylamino)naphthalene,[52] for example, has been attributed in part to relief of strain accompanied by protonation.

5-Methylbenzonorbornadiene 68 was used as a 1,3-dipolarophile with hopes of simplifying the proton nmr spectrum, and possibly producing a cryptaliine katenaluminium adduct 69. The neutral species 69



was again produced as an oily mixture and could not be isolated. Rather, the hydrochloride salt 70 and its isomer 70' were obtained and characterized as such. ^{13}C analysis clearly shows the expected presence

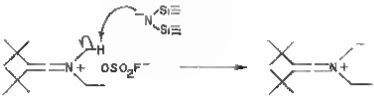


of isomers 70 and 70' as a series of line pairs, particularly in the aromatic region δ 120-150. The signals associated with the minor isomer, presumably 70', were based entirely on the relative intensity of each pair of lines. The lower intensity lines being assigned to the minor isomer. The 100 MHz proton nmr spectrum of 70 confirmed the exo configuration from coupling constant parameters. These values were,

as expected, very similar to those observed for 67. Because of the fused aromatic ring, a more complete analysis of coupling could be made. The results of this analysis are listed in Table V.

Discussion

The experimental observations of dimerization and stereospecific addition to norbornene can best be explained in terms of the ketoiminium ylid 71. Dimerization of 1,3-dipoles is not new, and several reports



(16)

60 71

of these are found in the literature.[53-55] Two mechanistic pathways accounting for dimerization can be envisioned: concerted 3+3 cycloaddition resulting from orthogonal approach to two ylids and a nonconcerted two step addition. These are illustrated as mechanisms A and B respectively in Scheme XII. Molecular models of each system show no appreciable difference in the amount of van der Waals repulsion experienced in their transition states. Even so, mechanism B seems

SCHEME XII

Mechanism A

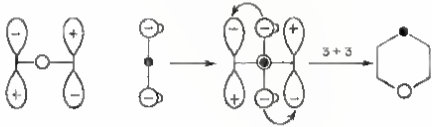
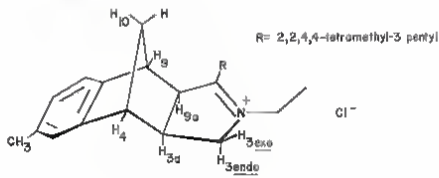


Table V

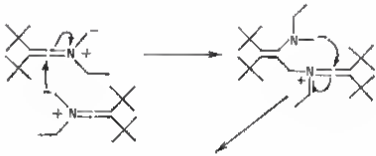
PMR Chemical Shift and Coupling Constant
Data for 70



70

Proton	δ	J	Calcd (Hz)	Obsd (Hz)
H_{10}	2.00	$J_{10,3a}+J_{10,3a}$	0-4[48,49]	4.0[48]
H_{3e}	2.86	$J_{3e,3e}$	8.0[46]	8.0
		$J_{3e,3endo}$	9.5[46]	10.0
		$J_{3e,3endo}+J_{3e,3exo}+J_{3e,4}+J_{3e,9a}+J_{3e,10}$	25(±1.5)[48,49]	22.0[48]
H_{9e}	3.50	$J_{9e,3e}$	8.0[46]	8.0
		$J_{9e,3e}+J_{9e,3exo}+J_{9e,4}+J_{9e,10}$	13.7(±1.5)[48,49]	14.0[48]
H_4	3.86	$J_{4,3e}+J_{4,9}$	2.2(±1.2)[48,49]	3.0[48]
H_9	3.96	$J_{9,9a}+J_{9,4}$	2.2(±1.2)[48,49]	3.0[48]
H_{3exo}	ca. 4.49-4.82			
H_{3endo}	4.95	$J_{3endo,3e}$	9.5[46]	10.0
		$J_{3endo,3exo}$	12-15[49]	15.0

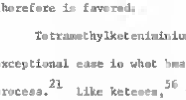
Mechanism B



63

unlikely. Considering the relative concentrations of the dipole 71 vs. the ketenimidium salt 60, a stepwise attack by the dipole on 60 should become a competing process if not the major one. No products were detected which could lend support to this mechanism. Mechanism A, therefore is favored.

Tetramethylketeniminium fluoroborate cycloadds to olefins with exceptional ease in what has been described as a $_{\pi}2_{s}+_{\pi}2_{a}$ concerted process.[21] Like ketenes,[56] the ability to accomplish this is due to strong bonding interactions between the electrophilic imidium cation and the π network of the olefin. The absence of steric hindrance and transition state strain inherent in typical olefinic systems are contributing factors, too.[57] It is logical to assume that this same



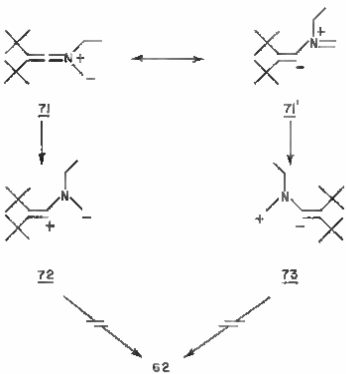
○ = Electrophilic iminium orbital

electrophilic bonding interaction is present to assist in the proper geometric orientation of ylide 71 prior to bonding. The electrophilic

interaction in this case would be with the anionic terminus of the ketenimidium ylid 71. This overall concerted process, then, could be classified as $_{\pi}4_{s}+_{\pi}4_{s}$ cycloaddition.

The failure to observe electrocyclic ring closure was perplexing at first scrutiny, since the requisite dipole almost certainly had been generated. A rationale for this apparent anomalous behavior is offered in Scheme XIII. For cyclization to occur, the dipole in either of its two valence bond resonance structures must necessarily pass through a transition state whose electronic environment can formally be described as 72 or 73. In either state, a high energy carbonium ion center[58] must be maintained throughout the cyclization until effective overlap can be achieved with the orbital carrying the

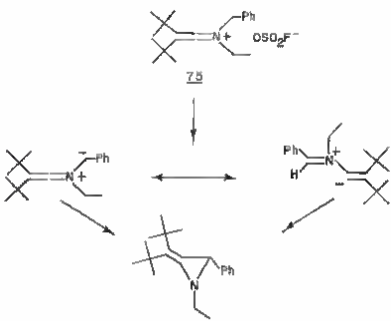
SCHEME XIII



negative charge. Although direct analogy from aziridine isomerizations was not found in the literature, it is known that substituents which can stabilize the incipient azomethine ylid facilitate the rapid reversible ring opening process. Aziridines lacking such substituents tend to sustain carbon-carbon or carbon-nitrogen bond scission and polymerize when subjected to thermal ring opening conditions.[59]

It would be of interest in future work in this area to consider the synthesis of ketoiminium salts bearing potential ylid stabilizing groups, particularly these incorporated as nitrogen substituents. An aromatic system, for example, could serve a twofold function: (1) to directly assist in the ring closure *via* conjugative stabilization of the ylid, and (2) to enhance the acidity of the protons adjacent to the iminium nitrogen.

SCHEME XIV



CHAPTER II

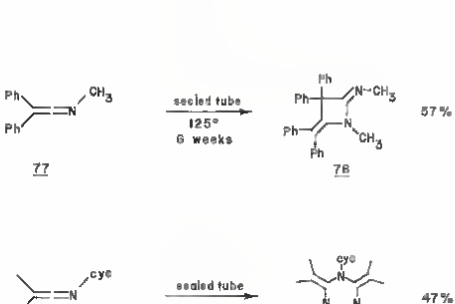
KETENIMINIUM FLUOROSULFONATE SALTS: OLIGOMERIZATION OF KETENIMINES BY METHYL FLUOROSULFONATE

Introduction

In Chapter I, it was shown that a sterically protected t-butyl ketenimine experiences facile and rapid alkylation with methyl fluorosulfonate to produce a stable, recrystallizable keteniminiu fluorosulfonate salt in high yield. Different results were obtained, though, when the bulk of the ketenimine substituents was reduced. In these cases, dimers and trimers were formed. Barker and Rosamond[60-62] have recently reported the thermal chemistry of various ketenimines. They suggested that specificity for dimer and trimer formation was based upon alkyl vs. aryl substitution. For example, ketenimines which thermally trimerize to any appreciable extent are the fully aliphatic substituted ketenimines; in contrast, 2-iminoazetidines appear to arise from diarylketene-N-alkylimines (Scheme XV). Systems with N-aryl functionality, unsubstituted in the ortho position, yield quinazolines (dimers) as the major product. No mechanistic conclusions or speculations were given by Barker in his publications.

The objective of this chapter, then, is to describe the oligomeric behavior of several ketenimines under strong alkylating conditions. Chronologically, this work preceded the results obtained in Chapter I. However, it was the informative chemistry and mechanistic implications to be discussed in this chapter that led to the eventual formation of the unprecedented ketenimiminium ylid 71. An attempt was made to

SCHEME XV



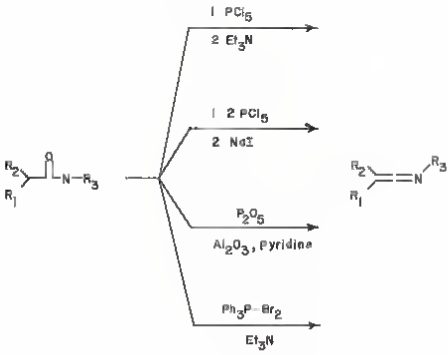
rationalize the specificity or selectivity of dimer and trimer formation in terms of substituent effects, thermodynamics, and mechanism. These parameters will be correlated with those reported by Barker, and possible mechanistic pathways will be discussed. Also, the use of N-chloroenamines

will be evaluated as sources of ketoniminium salts, and, thereafter, precursors to alkylidene azirdines through 1,3-dipolar intermediates.

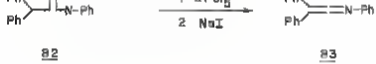
Results

The ketoniminas used in this work were prepared from their secondary amides according to several of the published procedures depicted in Scheme XVI.[29-32] The particular ketonimine substitution patterns needed for individual experimental design required no elaborate synthesis, since a wide variety of carboxylic acids and primary amines for the respective amides were commercially available.

SCHEME XVI



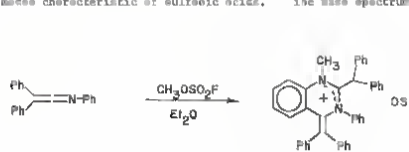
Alkylation of a dilute ethereal solution of diphenylketene-N-phenylimine 83 with methyl fluorosulfonate proceeded slowly. No



(17)

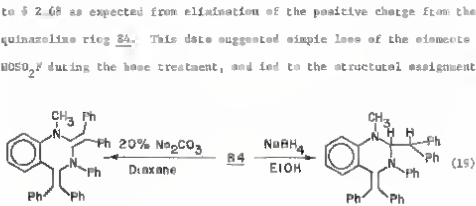
immediate color developments, generation of heat, or otherwise noticeable changes in the solution were observed until the first appearance of a clay colored precipitate nearly 60 minutes after the introduction of the methylating agent.

The nmr spectrum of this precipitated material showed a deshielded methyl resonance at δ 3.38 in addition to a profusion of aromatic signals. Integration of the methyl and aromatic signals confirmed a dimeric structure, and suggested a 2:1 adduct between ketenimine 83 and methyl fluorosulfonate respectively. The presence of the fluorosulfonate counterion (OSO_2F^-) was established by the appearance of infrared absorption maxima at 1275 cm^{-1} and 1065 cm^{-1}. These bands have been associated with the asymmetric and symmetric sulfur-oxygen vibrational modes characteristic of sulfonic acids.[63] The mass spectrum exhibited



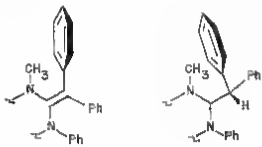
(18)

a pseudo parent ion at m/e 552 (P^{+}-$HOSO_2F$) with no major fragmentations other than the subsequent loss of 15 mass units ascribed to the cleavage of the N-methyl group. Spectral data and mechanistic extrapolations supported the quinazolinium structure 84. Since this was not sufficient basis for structural assignment, attempts were made at chemical degradation. Treatment of 84 with a 20% sodium carbonate solution in dioxane produced in near quantitative yield a brilliant fluorescent yellow compound. The high resolution mass spectrum of this material showed a parent ion at m/e 552.2581 (calcd for $C_{41}H_{32}N_2$: 552.2564), and a fragmentation pattern identical to fluorosulfonate salt 84. The nmr spectrum confirmed an upfield shift of the N-methyl signal from δ 3.38 to δ 2.68 as expected from elimination of the positive charge from the quinazoline ring 84. This data suggested simple loss of the elements $HOSO_2F$ during the base treatment, and led to the structural assignment 85.



Reduction of 84 with sodium borohydride proceeded vigorously and quantitatively to 86 which exhibited an AB quartet centered at δ 4.93. The N-methyl signal (δ 2.16) was found to be shifted approximately 0.5 ppm upfield from the position of the N-methyl signal in 85. Model compounds suggest that this shift is too large to attribute solely to saturation of the amasino functionality. The origin of this difference is undoubtedly the partial result of diamagnetic shielding by the

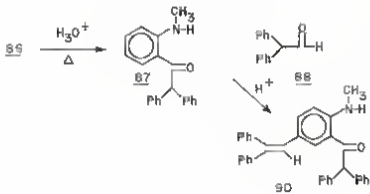
proximal aromatic ring. Examination of molecular models clearly shows that a greater degree of face to face interaction between the methyl group and the aromatic ring can be achieved in 86 (relative to 85). This argument is further substantiated by the spectral properties of a similar quinoxaline bearing no aromatic functionality in the 2-position. In this system (vide infra) the N-methyl resonance appears at δ 2.95;



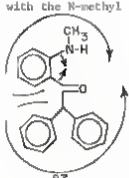
85' 86'

The reduced quinoxaline derivative 86 proved to be an ideal candidate for an unequivocal structure identification vie acid hydrolysis. Vigorous hydrolysis of 86 in refluxing hydrochloric acid produced the α-amino ketone 87 as a yellow oil in 75% yield, aniline, and trace amounts of diphenylacetaldehyde. Also, compound 90 was isolated as a yellow crystalline solid in approximately 24% yield. The presence of

SCHEME XVII



this material is presumably the result of acid catalyzed electrophilic substitution by diphenylacetaldehyde on the o-amino ketone 87 followed by dehydration. The structure 90 was established from its spectral properties. High resolution mass spectrometry of 90 showed a parent ion at m/e 479.2252 (calcd for $C_{35}H_{29}NO$: 479.2248). A base peak corresponding to the loss of a benzhydryl fragment appeared at m/e 312. A low frequency carbonyl stretching vibration attributed to intramolecular hydrogen bonding appeared at 1635 cm^{-1} in the infrared.[36,37] This value is slightly higher than the carbonyl band for 87 which is shifted 10 cm^{-1} lower to 1625 cm^{-1}. The nmr spectra of both 87 and 90 exhibit doublets (3H) at ca. δ 2.8 which collapse to singlets (3H) when washed with D_2O, and broad singlets (1H) at ca. δ 8.8 which completely disappear on similar treatment with D_2O. The extremely low field N-H resonances (ca. δ 8.8) are considerably lower than most reported o-amino aromatic ketones,[64] and are reflections of the strong intramolecular hydrogen bonding with the carbonyl oxygen.[37] A rationale for the abnormally low values of the N-H protons is not immediately obvious. Steric crowding between the benzhydryl and the amino ketone phenyl rings may cause the carbonyl group to "bow in" toward the amino substituent. This would allow for stronger hydrogen bonding and possibly account for the observed low field N-H resonances. This interpretation also explains the observed N-H coupling with the N-methyl protons which is the apparent



87

Result of retarded intermolecular N-H proton exchange.

While structural investigations into the above discussed quinazoline system were in progress, an ethereal solution of diphenylketene-N-(p-tolyl)imine 92 was alkylated under conditions similar to those used

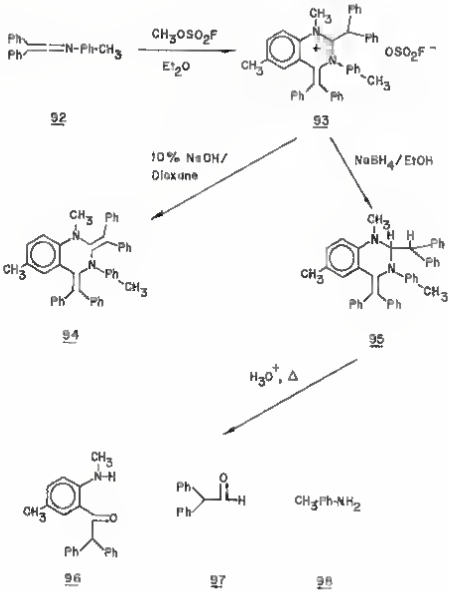
(20)

91 92

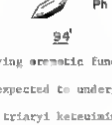
for 83, it was hoped that the methyl "labels" in the product would simplify spectroscopic data.

The alkylation and cyclization of 92 proceeded slowly with the gradual precipitation of the tan colored quinazolinium salt 93 in 84% yield. The structure and chemistry of this quinazolinium salt paralleled that for 84 and is shown summarized in Scheme XVIII. An interesting feature present in the nmr spectra of both 94 and 95 is the shielded C_6-methyl group which appeared at δ 1.92 and δ 1.84 respectively. The unusually high position of this signal was noted by comparison of the same resonance in a quinazoline derivative void of exocyclic aromatic substituents (vide infra). The source of this upfield shift (ca. 0.4 ppm) can again be attributed to diamagnetic shielding resulting from the canting of a benzhydrylidene phenyl group to a near orthogonal conformation relative to the quinazoline ring. Furthermore, a comparatively high field aromatic doublet (J=2 Hz, 1H) at δ 6.31 is observed in 94. This signal shows the correct multiplicity and coupling constant for the H_5 proton, and is well within the shielding environment

SCHEME XVIII

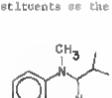


responsible for the C_6-methyl shift. In all likelihood, this same phenomenon is occuring in 95, but, unfortunately, overlapping aromatic signals made accurate assignments very difficult.



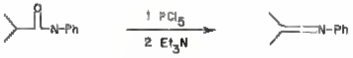
94'

Ketenimines carrying aromatic functionality only on nitrogen were examined. These were expected to undergo cyclization to quinazoline derivatives as did the triaryl ketenimines 83 and 92. Support for this anticipated behavior appeared in the literature [62] while this work was in progress. The principal reason for conducting these alkylations was to aid in the eventual structure elucidation of quinazoline derivatives 84 thru 94 which prior to this work were not firmly established. It was reasoned that a great portion of the analytical spectroscopic data of the triaryl ketenimine dimers was being obscured by the presence of "excess" aromatic signals. Further simplification could be achieved by replacing the phenyl substituents on the ketene terminus by alkyl groups.



99

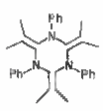
Thus, dimethylketene-N-phenylimine 29 was prepared as a greenish yellow oil from its amide precursor 100. Treatment of a dilute ethereal solution of this ketenimine with methyl fluorosulfonate produced after 24 hours a clear solution over a small amount of brown oil. The clear



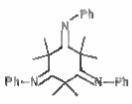
(71)

100 29

ethanate was separated from the oil and evaporated to a colorless crystalline solid (mp 163-164°). The mass spectrum of this compound showed major peaks at m/e 435 (indicative of a trimer) and 145, and a strong infrared absorption maximum at 1675 cm^{-1}. A singlet nmr resonance appeared at δ 1.44 for the methyl protons. This same trimer could be obtained in 60% yield by treating a dilute ethereal solution of dimethylketene-N-phenylimine 29 with a catalytic amount of chlorosulfonic acid. Singer, Davis, and Knutsen[65] reported a ketenimine trimer (mp 163-164°) isolated from the photolysate of 29 and acetone in a β-iminoketone synthesis. The trimer, identical in every respect to the one obtained in this work, could not be produced by unsensitized photolysis or thermolysis of the ketenimine alone. The compound was believed to be 101 or 102, but the authors claimed that the spectroscopic data alone was compatible with either structure. The system

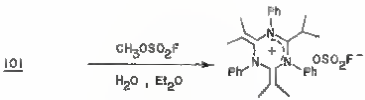


101



102

was not investigated further. In a later paper, Barker and Rosamond[61] assigned structure 102 to the trimer. Their arguments were based heavily on spectroscopic comparison of "somewhat analogous" systems and those of a trimer 80 derived from the thermolysis of dimethylketone-N-cyclohexylimine 79. Nevertheless, the trimer obtained in this work under alkylation conditions was assigned structure 101. It was found that if the ethereal alkylation product mixture containing 101 was exposed to atmospheric moisture, the yellow crystalline triazinium fluorosulfonate salt 103 was produced in 85% yield. This same product could be obtained as a chlorosulfonate salt by treating a carbon tetrachloride solution of triazine 101 with chlorosulfonic acid. The mass

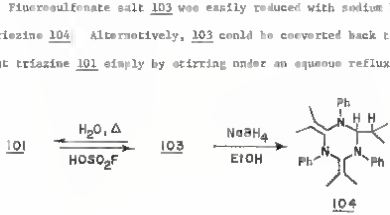


103 (22)

spectrum of 103 showed a pseudo parent ion at m/e 435 (P^+-$HOSO_2F$) and a fragmentation pattern identical to that of 101. A weak absorption band at 1640 cm^{-1} characteristic of most enamines[66] appeared in the infrared. The nmr spectrum in trifluoroacetic acid displayed a high field doublet at δ 0.74 (J=7 Hz, 6H), two six proton singlets at δ 1.38 and δ 2.06, a multiplet at δ 2.98 (J=7 Hz, 1H), and aromatic resonances in the region δ 7.1-7.8. A molecular model of 103 shows that the conformation needed to provide the upfield shift of the isopropyl and isopropylidene methyl protons is easily attained. The aromatic rings are virtually forced into a disposition orthogonal to the triazine ring as a result of steric repulsions with the nearby methyl groups

this shielding factor also applies to the high field resonance of the isopropylidene methyl protons (δ 1.44) found in 101. And, it is most likely partially responsible for the erroneous structural assignment made by Barker and Rosamond (*vide supra*).

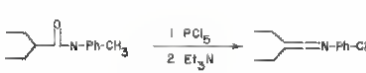
Fluorosulfonate salt 103 was easily reduced with sodium borohydride to triazine 104. Alternatively, 103 could be converted back to the parent triazine 101 simply by stirring under an aqueous reflux



(23)

The appearance of the isopropyl nmr pattern upon protonation and the reversible behavior toward protonation and deprotonation leave little doubt about the structure of 101. However, the conspicuous absence of a quinazoline and/or alkylated products in this system was difficult to rationalize. Clearly, the difference in product composition (*vs.* those observed for the triarylketenimines 83 and 92) could only be the result of substituent effects on the ketene terminus of the keteneimine, since this was the only modification made in the substrate. It was not clear,

though, whether the effects governing the cyclization process (dimer *vs.* trimer) were steric or electronic in nature. In order to clarify this point, diethylketene-N-(p-tolyl)imine 106 with increased bulk in the form of ethyl substituents on the ketene terminus was treated as an ethereal solution with methyl fluorosulfonate. After approximately



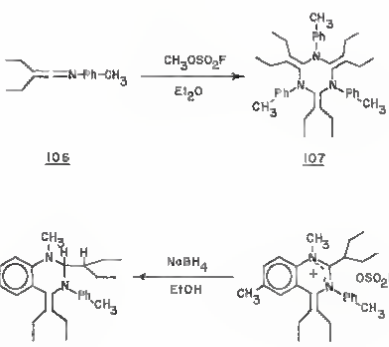
(24)

105 106

17 hours, the ethereate was evaporated to dryness, and the pasty residue diluted with ethanol. Moments later a colorless crystalline solid separated from the mixture. The mass spectrum of this material showed a parent ion at m/e 561.4086 (calcd for $C_{39}H_{51}N_3$, 561.4082), and a base peak at m/e 187. An enamine stretching vibration appeared in the infrared spectrum as a medium intensity band at 1640 cm^{-1}. These along with the appropriate signals in the nmr spectrum established the structure of this material as the trimer 107 (26%). The ethanolic filtrate from which the trimer 107 was crystallized was treated with excess sodium borohydride. The quinazoline derivative 109 was obtained from the product mixture as fine colorless needles in 34% overall yield. The mass spectrum revealed a parent ion at m/e 390 3031 (calcd for $C_{27}H_{38}N_2$ 390.3034), and a base peak at m/e 320, presumably resulting from the loss of the 3-pentyl fragment from the 2-position of 109. Included in the nmr spectrum were singlet methyl resonances at δ 2.15, 2.22, and 2.95, and a doublet at δ 4.76 (J=8 Hz, 1H, H_2). In the aromatic region, an ortho (from the N-methyl nitrogen) shielded proton appeared at

δ 6.32 (doublet, $J_{7,8}$=8 Hz) as well as a low field resonance at δ 7.38 (doublet, $J_{5,7}$=2 Hz, 1H, H_5) The relative ratio of triazine to

SCHEME XIX



106 107 108 109

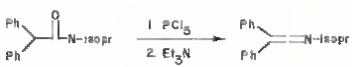
quinazoline in this system (1:1.3) suggests that dimerization is just becoming the kinetically preferred pathway.

From the product distribution observed in the N-aryl ketoimine systems investigated thus far, certain trends are clearly evident: (1) systems carrying substituents with bulk appreciably larger than ethyl (eg. phenyl, p-tolyl) favor quinazoline products exclusively, (2) smaller groups such as methyl tend to direct the cyclization to triazine derivatives, and (3) groups of intermediate size can be expected to

produce mixtures containing quinazolines and triazines of varying composition.

Attention was focused on N-alkyl ketenimines. Here, the possibility of cyclization through a nitrogen substituent would be entirely eliminated. In addition, the nitrogen should become somewhat more basic than the N-aryl derivatives, and, consequently, improve the chances of alkylation and isolation of a monomeric keteniminium salt.

Diphenylketene-N-isopropylimine 111 was prepared by the dehydrochlorination of the imidoyl chloride derived from 110. Alkylation of a



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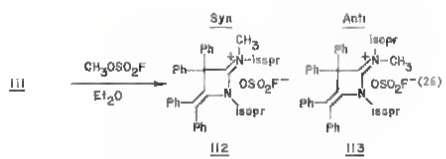
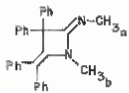
dilute ethereal solution of 111 with a two fold excess of methyl fluorosulfonate produced a mixture of syn and anti 2-iminoazetidinium fluorosulfonate salts 112 and 113 in approximately 80% yield. The



(26)

relative ratio of the two isomers was determined by integration of their magnetically nonequivalent N-methyl signals which were found at δ 2.82 (syn, ca. 20%) and δ 3.39 (anti, ca. 80%). The nmr spectrum was peculiar in other respects, and, therefore, warrants further

interpretation. The N-methyl resonance at δ 2.82 appears at an unusually highfield compared to positively charged Schiff bases containing N-methyl substituents.[18,67] This signal is even higher than the imino methyl resonance observed by Barker and Rosenand[60] for the diphenylketene-N-methylimine dimer 78. The magnitude and direction of this shift is

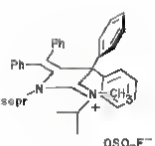


	δ
CH_{3_a}	2.94
CH_{3_b}	2.67

78

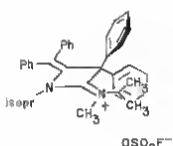
explicable only in terms of diamagnetic shielding from a nearby aromatic ring, since steric compression effects which could conceivably be present result only in paramagnetic shifts. Molecular models of the syn isomer 112 show the phenyl rings in the 3-position properly disposed to offer a diamagnetic shielding environment. This same effect is experienced by the isopropyl methyl protons in the anti

Syn



112

Anti



113

isomer 113 and is observed spectrally in the upfield shift to δ 0.[illegible]. Apparently, the isopropyl group on the azetidine ring nitrogen is unaffected by the aromatic systems and shows an unperturbed doublet at δ 1.42.[68] The high integration of this doublet results from the fortuitous superimposition of the imidium isopropyl resonance from the syn isomer 112. The effect, then, is a 20% increase over the intensity of a six proton isopropyl pattern. And, as a consequence, the high field isopropyl signal at δ 0.83 of the anti isomer 113 is only 80% as intense as a full six proton isopropyl doublet (cf. figure 3).

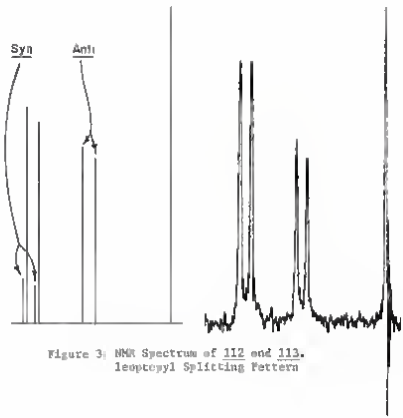


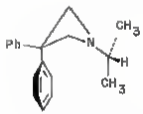
Figure 3: NMR Spectrum of 112 and 113. Isopropyl Splitting Pattern

The azetidinium isomers 112 and 113 were quantitatively reduced with sodium borohydride to a colorless crystalline solid which was identified as the neutral 2-aminoazetidine 114. Its mass spectrum showed a parent ion at m/e 486.3022 (calcd for $C_{35}H_{38}N_2$: 486.3034).

(27)

and a base peak at m/e 344 corresponding to a tetraphenylallene fragmentation.[60,69] The nmr spectrum contained a singlet at δ 5.42 which was assigned to the azetidine ring proton. The N-methyl and N-isopropyl methyl signals, however, again were affected by diamagnetic shielding. The N-methyl resonance appeared at δ 1.57 while a pair of isopropyl doublets (9H and 3H) were found at δ 0.95 and δ 1.16 respectively. Inspection of molecular models clearly shows the ease with which the methyl and isopropyl groups of the exocyclic nitrogen can freely rotate about the face of a proximal phenyl group in the 3-position. This accounts for their upfield shifts. Also, a shielding environment for the azetidinyl isopropyl protons is available provided rotation about the carbon nitrogen bond is completely unhindered. Molecular models, though, indicate considerable steric interactions between the adjacent benzhydrylidene phenyl ring and the isopropyl methyl group occurs when full rotation is attempted. It is suggested that hindered rotation results in a preferred conformation - at least on the nmr time scale - such that one methyl resides in the shielding cone of the ends

3-phenyl substituent while the other does not. The net effect would permit three of the four isopropyl methyls to experience shielding from



114'

nearby aromatic systems while the fourth would be relatively unperturbed. This analysis is in agreement with the 3:1 integration ratio of the two sets of isopropyl signals. Further evidence for the magnetic nonequivalence of the azetidinyl isopropyl methyls is found in the nmr spectrum of 114 taken in pyridine (cf. figure 4). Here, three sets of doublets appear

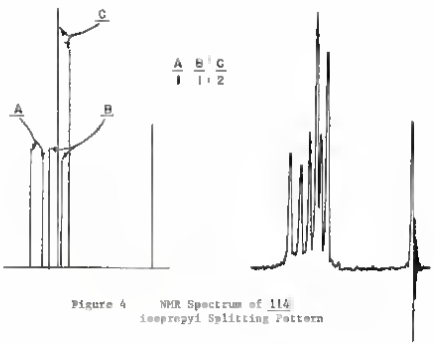
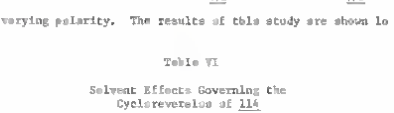


Figure 4 NMR Spectrum of 114
Isopropyl Splitting Pattern

in the ratios 1:1:2. The two smaller sets presumably correspond to the nonequivalent azetidinyl isopropyl methyl signals.

Thermolysis of a dry sample of 114 at ca. 125° resulted in an extremely facile ring fission to tetraphenylallene 115 and the formamidine 116. Subsequently, a solvent dependence study was conducted in media



(28)

of varying polarity. The results of this study are shown in Table VI.

Table VI

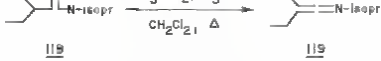
Solvent Effects Governing the Cycloreversion of 114

Solvent (5 minutes @75°)	Azetidine	Formamidine
pyridine	1.0	1.0
methylene chloride	1.1	1.0
chloroform	2.1	1.0
benzene	3.5	1.0
toluene	3.6	1.0

The trend clearly indicates a marked preference for solvents of higher polarity, and, consequently, rules out a concerted 2_s+2_s process. Dipolar cycloreversions of substituted cyclobutanes are known to be strongly solvent dependent and show the greatest increases in rate in those solvents which are better able to solvate the zwitterionic intermediate.[70] The data obtained in Table VI are consistent with this type of dipolar

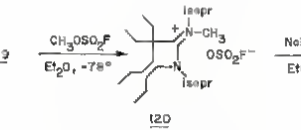
ring opening. Attempts to intercept the presumed "zwitterion" 117 with either ethanol or dimethylacetylenedicarboxylate still led to a clean conversion to 115 and 116.

In a final system, the trialkylketenimine 119 was prepared as a colorless hygroscopic liquid from its amide precursor 118. Treatment



of a dilute ethereal solution of 119 with methyl fluorosulfonate at room temperature resulted in a vigorous reaction which yielded a complex product mixture. Nmr analysis of the oily mixture showed no methyl signal in the region δ 3.0-4.0 which could be attributed to an alkylated product. Low temperature alkylation with freshly distilled methyl fluorosulfonate, however, resulted in a much smoother and cleaner reaction. The oily product mixture, presumably containing the azetidinium salt 120, was reduced immediately with excess sodium borohydride. The product obtained had the appropriate nmr signals and infrared bands for the azetidine 121. However, attempts to purify the

crude azetidine either by chromatography or I.R. to 1-H- distillation resulted in some product decomposition and only slight purification. High resolution mass spectrometry of a distilled sample of 121 showed a parent ion at m/e 294.3037 (calcd for $C_{19}H_{38}N_2$: 294.3034) and major peaks at m/e 154 and 111. A potential mechanistic pathway for ring



(31)

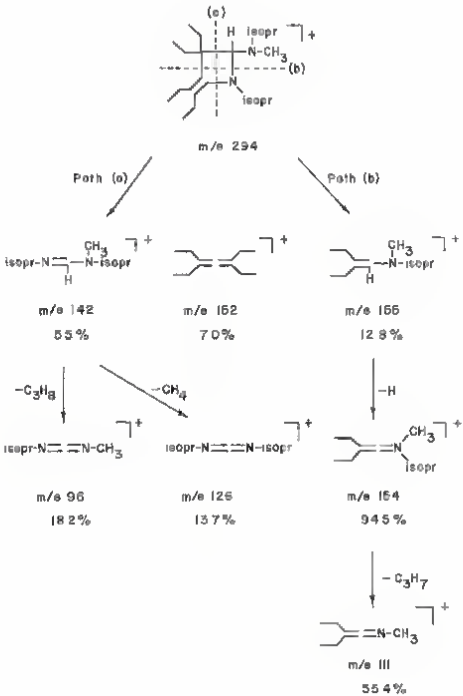
fission and fragmentation is illustrated in Scheme XX

The azetidine 121 demonstrated no tendency to under go a facile dipolar cycloreversion as did 114. This was borne out by its ability to survive vacuum distillation (bp 95-100°/0.75 mm Hg) without appreciable change.

Discussion

It was demonstrated in this chapter that the formation of quinazolines and triazines from N-aryl ketoimines under strong alkylation conditions was dependent upon the size of the substituents carried on the ketone terminus of the ketoimine substrate. The systems with the greatest degree of bulk formed quinazoline derivatives exclusively while those with much smaller groups gave only triazines in order to propose a meaningful mechanism which will effectively account for both products under the same conditions, one must consider further experimental facts: (1) the trimerization of dimethylketone-N-phenylimine 29 was found to occur either with methyl fluorosulfonate or

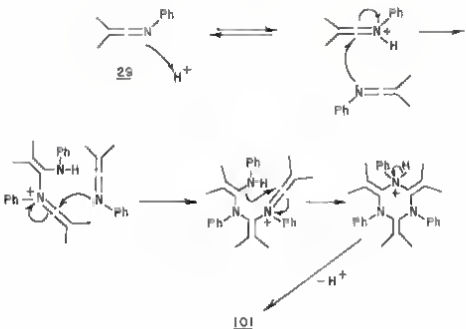
SCHEME XX


(a)
H
isopr
N-CH3
(b)
N
isopr
m/e 294
Path (a)
Path (b)
isopr-N
CH3
N-isopr
H
m/e 142
55%
m/e 152
70%
CH3
N-isopr
H
m/e 166
12.8%
-C3H8
-CH4
-H
isopr-N
N-CH3
m/e 96
18.2%
isopr-N
N-isopr
m/e 126
13.7%
CH3
N
isopr
m/e 154
94.5%
-C3H7
N-CH3
m/e 111
55.4%

in the presence of trace amounts of mineral acid, (2) no evidence of a methylated product was detected in this system, (3) the formation of both triazines and quinazolines required fairly lengthy exposure to the alkylating agent to effect product formation, (4) quinazolines were the only methylated products recovered from N-arylketenimine systems, and (5) the alkylation of N-alkyl ketenimines proceeded rapidly with high conversions to methylated products.

The acid catalyzed cyclization of N-aryl ketenimines to triazines most likely proceeds with reversible protonation of nitrogen to form a ketenimininium fluorosulfonate salt as depicted in Scheme XXI. Subsequent ketenimine addition to the activated iminium carbon[19-23] followed by

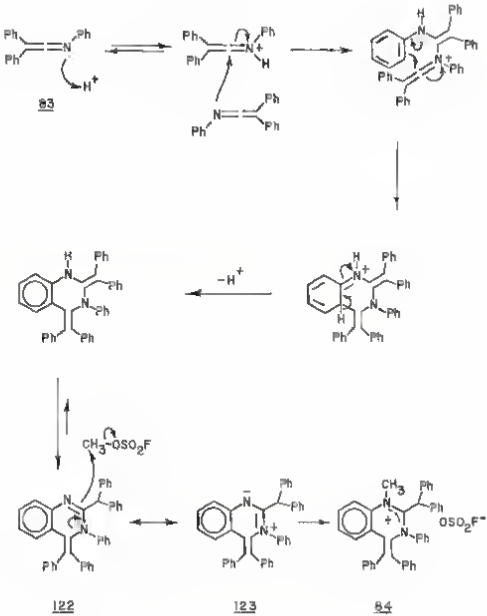
SCHEME XXI



ions of the proton catalyst results in the observed triazine 101. The proton source is methyl fluorosulfonate could arise from small amounts of hydrolysis which would be expected to produce methanol and fluorosulfonic acid. Hartke, Rassbach, and Raden[71] have proposed a similar mechanism for the cyclization of dialkyl carbodiimides to imino-azetidines (catalyzed by tetrafluoroboric acid). The reluctance of ketenimines 29 to undergo alkylation suggests a similar mechanism in the triaryl ketenimine systems. If the failure to observe alkylation is a function of electronic demand at nitrogen, and it probably is, then the triaryl systems would, by virtue of the electronic withdrawing capacity of phenyl groups, tend to be even more resistant. The proposed mechanism for the cyclization of N-aryl ketenimines to quinazolines is illustrated in Scheme XXII. The initial pathway to quinazoline 122 would be an acid catalyzed process as shown. There is literature precedent for this type of behavior with diaryl carbodiimides which cyclize under acidic conditions to quinazolines.[71] The nucleophilicity of 122 relative to 83 would seem to be greatly enhanced by the resonance contribution of the nitrogen in the 3-position. Alkylation at the 1-position[72] should take place easily to produce 84.

The comparative behavior of the N-aryl ketenimine systems in this work with those of other workers is interesting. The major product obtained by Barber and Rasmussen[62] from the thermolysis of dimethylketene-N-phenylimine 29 was the quinazoline 31. In addition, an unidentified trimer was determined by gc/ms to constitute approximately 20% of the product mixture. Unfortunately, the identity of this trimer was not established. The high percentage of dimer (76% vs. 20%) in Barber's system in puzzling, since no trace of a quinazoline was detected when the

SCHEME XXII



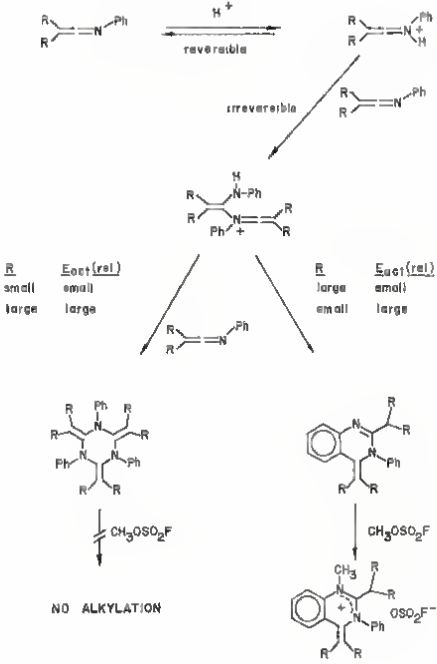
same ketenimine 29 was treated at room temperature with methyl fluorosulfonate Differences in experimental parameters such as solvent, trace

acid concentration, solvent ion and temperature are expected to influence the course of reaction. In Barker's work, for example, the cyclization of ketenimines were effected at 125° in a sealed tube without a solvent. Obviously, these differ considerably from the conditions described in this work. Such a dramatic contrast in product distribution, though, may reflect a difference in activation energy for cyclization. If the energy of activation for cyclization to quinazoline is high with respect to trimerization, room temperature cyclization would be expected to favor the trimer as it did in this work. At higher temperatures, though, the two processes become competing and the thermodynamically more stable product (presumably the quinazoline 81) becomes dominant as it did in Barker's work. This hypothesis could be tested by simply conducting the alkylation of ketenimine 28 with methyl fluorosulfonate at higher temperature. The preparation of a quinazolinium fluorosulfonate salt would confirm the supposition.

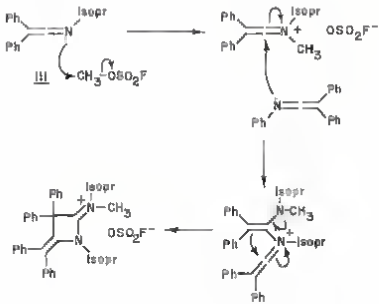
In the case of triaryl ketenimine, the activation energy for dimerization must be low with respect to that for trimerization. This is conceivable if one considers the relative amounts of phenyl-phenyl repulsions experienced in each system. Clearly, the quinazoline suffers less from such interactions than the corresponding trimer. These arguments are summarized in Scheme XXIII.

The formation of azetidines from N-alkyl ketenimines under alkylation conditions is more likely to be occurring *via* direct methylation of the ketenimine nitrogen. Support for this contention is found in the case with which di-t-butylketene-N-ethylimine 59 (Chapter I) was alkylated with methyl fluorosulfonate. Also, a mechanism analogous to the one illustrated in Scheme XXIV has been proposed for

SCHEME XXIII



SCHEME XXIV



112 , 113

the cyclization of N-alkyl carbodiimides to iminodiazetidines.[71] The azetidinium fluorosulfonate salts 112 and 113 bear similarity to the 2-iminoazetidine 78 reported by Barker and Rosamond[60] from the thermolysis of diphenylketene-N-methylimine. In a later paper they observed the trimerization of dimethylketene-N-cyclohexylimine 80[61] under essentially the same thermolytic conditions. To this date, however, no advances have been made concerning the mechanism of these thermolytic processes. For the most part, the product distribution of

the heterocycles formed through thermolytic closely parallel those obtained in this work under strong alkylating conditions. It is this author's belief that trace acid catalysis is responsible for all the heterocyclic dimers and trimers obtained under thermolytic conditions. The proton source could easily arise from trace amounts of hydrogen chloride picked up by the ketenimine during synthesis, since all of the ketenimines used by Barker and Rosemond[60-62] were prepared from the dehydrochlorination of imidoyl chloride precursors. Indeed, in two instances,[60,61] respective dimers and/or trimers were isolated and characterized from ketenimine distillates obtained during preparative work-up.

The cyclization of diethylketene-N-isopropylimine 119 to its corresponding azetidine 121 would proceed by the mechanism already described in Scheme XXIV. The failure to isolate or detect a trimer from this system is probably indicative of rapid irreversible alkylation of the ketenimine nitrogen. Once alkylation has taken place, ring closure to a triazine of the type described in this work is effectively eliminated.

α-CHLOROENAMINES

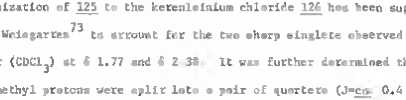
Introduction

Recent reports concerning the conversions of α-chloroenamines to ketenimidium tetrafluoroborate salts[19-23] has prompted this investigation into the response of these systems to sterically hindered strong bases, eg. potassium t-butoxide and sodium bis(trimethylsilyl)amide. It was hoped that deprotonation could be effected by these bases, and provide a relatively straightforward route to ketenimidium ylide 42.

These ylide in turn would have the potential of undergoing electrocyclic ring closure[18] to the intermediate alkylidene aziridine series.

Results

α-Chloroenamide 125 was prepared as a hygroscopic, photosensitive colorless liquid from its amide precursor 124. A rapid reversible



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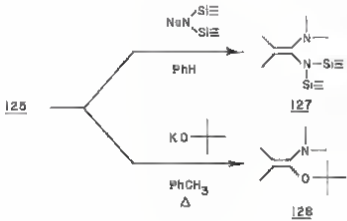
124 125 126

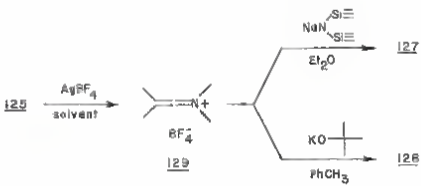
ionization of 125 to the ketenieminium chloride 126 has been suggested by Weingarten[73] to account for the two sharp singlets observed in the nmr ($CDCl_3$) at δ 1.77 and δ 2.38. It was further determined that the C-methyl protons were split into a pair of quartets (J=ca. 0.4 Hz) centered at δ 1.71 and δ 1.69 when examined in the aromatic solvents benzene-d_6 or toluene-d_8. This data was interpreted as a shift in the equilibrium to that favoring the covalent structure 125. Long range coupling between the nonequivalent C-methyl protons would account for the splitting pattern.[41]

Attempts were made to effect deprotonation of 125 with either sodium bis(trimethylsilyl)amide or potassium t-butoxide. The reactions were carried out in benzene or toluene, since most polar solvents would hardly be stable under the strongly basic conditions. Adducts 127 and 128 were obtained as major products along with N,N-dimethylisobutyramide 124, presumably from hydrolysis of unreacted 125 during the course of work-up. Displacement by the silylamide occurred smoothly at room temperature to give 127 in approximately 70% yield. Attack



(34)

by t-butoxide, however, took place much more slowly at room temperature, and even after 20 hours under refluxing toluene only ca. 40% conversion to 128 was estimated from nmr analysis of the crude product mixture. The only other identifiable product was amide 124 which codistilled with 128. Similar attempts at deprotonation were made with the fluoroborate salt 129. Here, again only 127 and 128 were produced along with



expected small amounts of amide 124. The additions to 129 proceeded much more rapidly than with the α-chloroenamine 125 as would be anticipated of a compound containing an imidoyl carbon.[19-23] It was hoped, however, that deprotonation would become a competing process. Unfortunately, there is no simple method for determining whether deprotonation is being achieved. Virtually all 1,3-dipolarophiles which could be used to intercept the dipole would be unstable either to the strongly basic conditions needed for proton abstraction[18] or to the electrophilicity of the ketoiminium salt 129.[19-23] Quenching experiments with D_2O would not serve well, since only a small steady state concentration of ylid 42 is to be expected at any given time.[18]

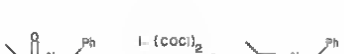
Attention was focused on the synthesis of α-chloroenamines sterically protected at the α-positions. Protection of this nature might discourage attack by base to form addition products similar to 127 and 128, and perhaps direct the course of reaction towards deprotonation. Thus, the diphenyl derivative 131 was prepared by vigorous treatment of amide 130 with phosphorous pentachloride in refluxing benzene followed by dehydrochlorination with triethylamine. The α-chloroenamine 131

130 131 77

was obtained in 47% yield as a viscous yellow oil. This material proved to be very hygroscopic and quite difficult to purify, however, trituration into hexane appeared to be the best technique for removing amide 130 impurities. Treatment of α-chloroenamine 131 with a benzene

slurry of sodium bis(trimethylsilyl)amide produced a deep reddish brown product mixture which showed an intense infrared absorption maximum at 2000 cm^{-1}. This band is very characteristic of a ketenimine functionality and most likely arises from the dealkylation of 131 to diphenylketene-N-methylimine 77. Dayrup and Szabo[18] have observed similar dealkylations when treating ternary iminium fluorosulfonate salts with this same silylamide base.

Increasing the acidity of the protons carried by the nitrogen substituents was considered to be yet another alternative. The N-benzyl α-chloroenamine 133 was prepared as a hygroscopic yellow liquid in 68% yield from its amide precursor 132. Because of inductive resonance effects of the phenyl group, the benzyl protons of 133 should be somewhat more acidic than those of the N-methyl. Disappointingly, as



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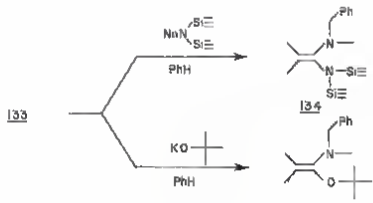
132 133

products were obtained under deprotonation conditions which could have been the direct result of initial proton abstraction. Instead, only adducts 134 and 135 along with smaller amounts of amide 132 were recovered from the product mixture. The silylamide product 134 was isolated in 66% yield while the t-butoxy derivative 135 was obtained as a mixture with amide 132 in the approximate molar ratio of 3:2:1 respectively.

In a final effort to construct an α-chloroenamine with appreciably acidic protons adjacent to nitrogen, the N-carbethoxymethyl amide 138



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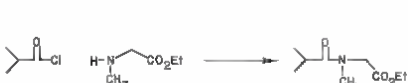
(40)

was synthesized via the condensation of ethyl N-methylglycinate 137 with isobutyryl chloride 136. The conversion of 135 to the α-chloroenamine 138 was effected by the usual methods, but only in ca 23% yield.

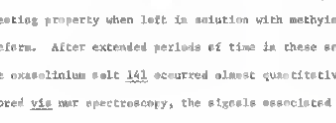


(41)

This hygroscopic colorless liquid exhibited infrared maxima at 1735 and 1640 cm^{-1} corresponding to stretching modes of the ester carbonyl and enamine functionalities respectively. The C-methyl resonances of the enamine appeared as sharp singlets at δ 1.72 and δ 1.85 in carbon tetrachloride, but broadened noticeably when examined in chloroform in addition to the expected ethyl pattern at δ 1 23 (triplet) and δ 4.08 (quartet), N-methyl and N-methylene singlets were

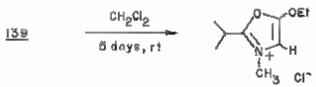
(42)

observed at δ 2.47 and δ 3.27 respectively. When the α-chlorosenamine 139 was treated with potassium t-butoxide in anhydrous ether for 12 hours under a nitrogen atmosphere, a mixture was obtained whose gross nmr spectral properties were essentially identical to those of amide 138. Other resonances appeared at δ 1.63 (doublet, ca. 6H), 2.43 (singlet, ca. 3H) and 5.63 (singlet, ca. 1H), but represented only a small amount (<5%) of the total product mixture. These signals could correspond to the



(43)

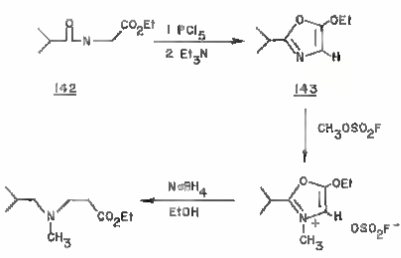
isopropylideneoxazoline 140. Due to the large amount of contamination, and the small amount of material at hand, attempts to isolate this component were not undertaken. The α-chlorosenamine 139 exhibited an interesting property when left in solution with methylene chloride or chloroform. After extended periods of time in these solvents, cyclization to the oxazolinium salt 141 occurred almost quantitatively. When monitored via nmr spectroscopy, the signals associated with 139 gradually disappeared, and, finally, were completely replaced by resonances



(64)

at δ 1.47 (doublet, J=7 Hz), 1.52 (triplet, J=7 Hz), 3.88 (multiplet, J=7 Hz), 4.27 (singlet), 4.44 (quartet), and 8.25 (singlet). Accurate integration of these signals was not possible due to the overlapping of residual amide 138 resonances present as a result of hydrolysis of 139. In order to unequivocally establish the structure of 141, the 5-ethoxyoxazole 143 was prepared by converting the amide 142 to its imidoyl chloride and subsequent dehydrochlorination with triethylamine. This

SCHEME XXV



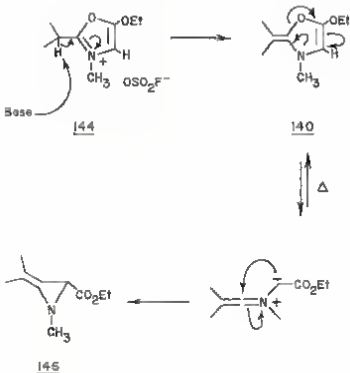
oxazole was identical in every respect to that reported in the literature by another method.[74] Methylation of 143 in anhydrous ether with methyl fluorosulfonate was effected smoothly and in high yield. This material exhibited an infrared absorption band at 1670 cm^{-1} and nmr signals at δ 1.41 (doublet, J=7 Hz, 6H), 1.47 (triplet, J=7 Hz, 3H), 3.52 (heptet, J=7 Hz, 1H), 3.85 (singlet, 3H), 4.30 (quartet, J=7 Hz, 2H), and 5.93 (singlet, 1H). The positions of these signals are quite similar to those of 111 with the exception of the vinyl resonance which appears at the very low value of δ.25. No rational explanation can be offered for the difference in the chemical shifts of the vinyl protons. It is difficult to ascribe the magnitude of this difference merely to a difference in counterion, but other than this the two systems appear to be identical. Furthermore, sodium borohydride reduction of 141 and 139 give the same N-methyl-N-isobutylglycinate 145.

The heterocycle 144 is of interest, too. Simple deprotonation of this oxazolidium salt could lead to a product discussed earlier and thought to be 140 (vide supra). The thermolytic behavior of 140 has not been investigated. However, it appears to have the potential of manifesting itself as a Cornforth type[75] ring opening to the ketoiminium ylid, and, possibly, closure to the isopropylidene aziridine 146.

Discussion

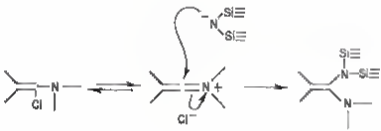
The utility of α-chloroenamines as precursors to ketoiminium ylids 42 is limited for several reasons: (1) the ease with which nucleophilic displacements occur at the vinyl carbon to form adducts under deprotonation conditions, (2) the difficulties encountered in synthesizing sterically protected derivatives, and (3) the apparent low acidity of the protons adjacent to nitrogen. The facile displacement

SCHEME XXVI



of chloride at the vinyl carbon by a sterically hindered nonnucleophilic base was surprising in view of the fact that vinyl substituents are normally very resistant toward substitution.[76] This anomalous observation is explicable in terms of a pre-ionization to the ketoniminium salt 126 as illustrated in Scheme XXVII. This pre-ionization mechanism could also explain the cyclization of 139 to its oxazolinium chloride salt 141. Interestingly, this cyclization proceeds in methylene chloride or chloroform, but not in other polar solvents such as acetonitrile or chlorobenzene.

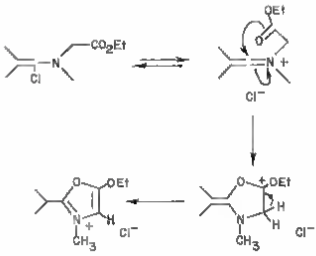
SCHEME XXVII



125 126 127

Even the addition of hydrogen chloride which is known to be present in chlorinated solvents failed to induce cyclization. Apparently, other differences in these solvents are responsible for this rather novel transformation. In any case, more work is required to determine the subtle effects of solvent media upon cyclization.

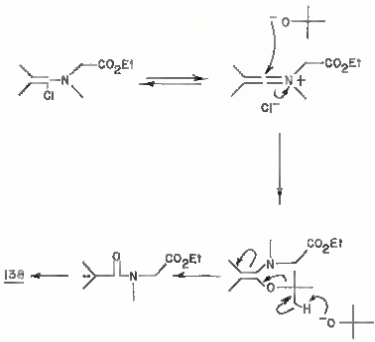
SCHEME XXVIII



141

The large amount of amide 138 detected in the product mixture resulting from the attempted deprotection of 139 with potassium t-butoxide was perplexing despite the use of anhydrous solvents and efforts to maintain a moisture free environment. It is true that atmospheric moisture could have been responsible for its formation, however, one cannot overlook the possibility of a deprotonation mechanism illustrated in Scheme XXIX [9]

SCHEME XXIX

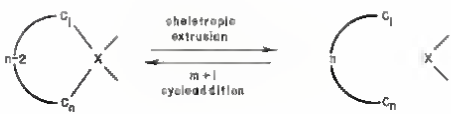


CHAPTER III

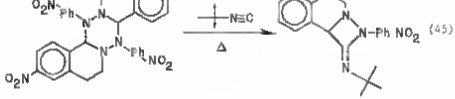
ADDITIONS OF t-BUTYLISONITRILE TO AZIRIDINES

Cheletropic reactions are concerted reactions characterized by the formation or cleavage of two sigma bonds terminating at a single atom (Scheme XXX).[57] Familiar examples include small molecule

SCHEME XXX



extrusions and carbene as well as nitrene additions to olefins. Cheletropic cycloadditions of a 3+1 type are extremely rare.[77] The most recent report of a 3+1 adduct involved the addition of t-butylisonitrile to the hexahydrotetrazines 147 with formation of the imino diazetidine 148.[78] Although the reaction almost certainly proceeded via the 1,3-dipolar azomethine imine intermediate, no conclusions could be drawn concerning the concertedness of the addition of the isonitrile to the dipole. Since the properties of 147 and 148 did not lend themselves to a detailed mechanistic study, systems were sought after which were likely to undergo such cycloadditions and which might be mechanistically informative.



147 146

Functionally substituted aziridines bear close analogy to azomethine imine precursors with respect to their ability to undergo thermal or photolytic ring opening to their 1,3-dipolar states. Also, cycloadditions of aziridines with suitable 1,3 dipolarophiles are known to take place in a concerted fashion,[43-45] and have been shown to conform with orbital symmetry requirements advanced by Woodward and Hoffmann[57]

Assuming a 3+1 adduct is formed between a 1,2,3-trisubstituted aziridine and t-butylisonitrile 9, one could expect to find two possible adducts (149 and/or 150). The mechanistic pathway, of course, will dictate the product distribution. This will be dependent upon several

149 150

factors: (1) a concerted *vs.* a stepwise addition, (2) the configuration (*cis*, *trans*) of the aziridine,[43,44] (3) the rate of cycloaddition relative to that of aziridine isomerization,[43,44] and (4) the experimental conditions.

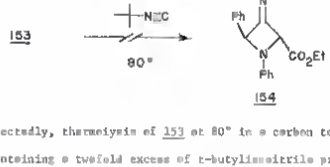
The functionalized aziridine system was chosen because ring opening to its azomethine ylid has been demonstrated to be clean, reversible, and not complicated by troublesome side reactions. Furthermore, the small number of protons on the aziridine ring (and eventually on 149 and 150) would allow easy access to mechanistic studies *via* nmr spectroscopy.

Results

The aziridine chosen in this work for the purpose of generating a 1,3-dipolar intermediate was ethyl *trans*-1,3-diphenyl-2-aziridinecarboxylate 153. Its synthesis was accomplished according to equation (46) by an already published procedure[79] Aziridine 153 was shown to

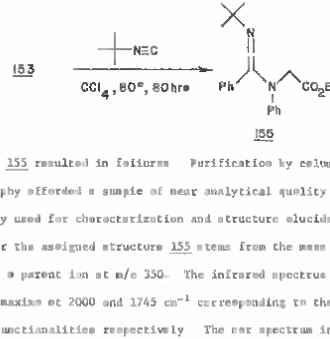
161 152 153 (46)

equilibrate easily in refluxing carbon tetrachloride to an approximate 65:35 *cis*:*trans* isomeric distribution. Treatment of aziridine 153 with t-butylisonitrile 9 in a sealed tube for 24 hours at 80° disappointingly produced no adduct with the isonitrile. However, spectroscopic investigation of the reaction mixture showed that the aziridine had indeed isomerized to a *cis*:*trans* mixture. It was thus established that the azomethine ylid had been formed and failed to react.



(47)

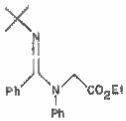
Unexpectedly, thermolysis of 153 at 80° in a carbon tetrachloride solution containing a twofold excess of t-butylisonitrile produced ketenimine 155 as a golden oil in 92% yield.[80] Repeated attempts to



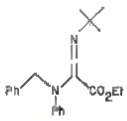
(48)

crystallize 155 resulted in failure. Purification by column chromatography afforded a sample of near analytical quality which was subsequently used for characterization and structure elucidation. Evidence for the assigned structure 155 stems from the mass spectrum which shows a parent ion at m/e 350. The infrared spectrum displayed absorption maxima at 2000 and 1745 cm^{-1} corresponding to the ketenimine and ester functionalities respectively. The nmr spectrum included a two proton singlet at δ 4.16 superimposed over a two proton quartet centered at δ 4.13. These data, however, do not unequivocally rule out the possibility of the isomeric ketenimine 156.

Spectral properties of suitable model compounds in the form of chemical shift data of the methylene protons of 157 and 158 suggested

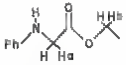


155



156

leaner 156 as the more plausible structure It might be expected, however, that the inductive effect of the ketenimine functionality in conjugation with the nitrogen lone pair in both structures 155



157

158

Nmr Ha = δ 3.78 Hc = δ 4.22

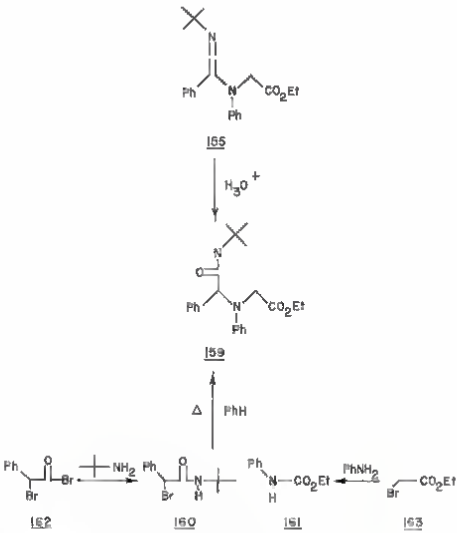
Hb = 4.13

IR C=O = 1736 cm^{-1}

and 156 should have a slight deshielding effect on the methylene protons in either case. If this assumption is correct, model compound 157 would be more compatible with the experimental data, and thereby be in agreement with the assigned structure 155.

Further and unambiguous structural confirmation was obtained from the acid catalyzed hydrolysis of ketenimine 155 to amide 159, and the subsequent synthesis of 159 from 2-bromo-2-phenyl-N-t-butylacetamide 160 and ethyl N-phenylglycinate 161 as outlined in Scheme XXXI. The

SCHEME XXXI



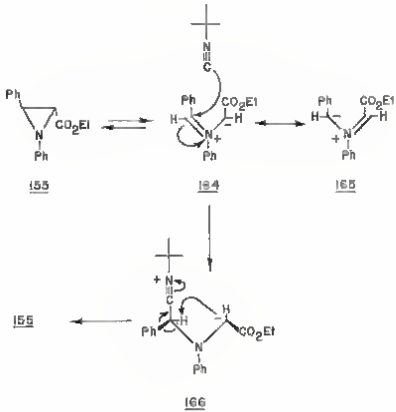
2-phenyl-2-(N-phenyl-N-carbethoxymethyl)amino-N'-t-butylacetamide 159 obtained by each synthesis displayed identical properties in their infrared and nmr spectra.

Discussion

The origin of ketenimine 155 can be rationalized on the basis of two mechanistic pathways. The first, illustrated in Scheme XXXII as mechanism A, involves the reversible ring opening of aziridine 153 to 164. Attack by t-butylisonitrile in a stepwise additive would most likely occur at the apparently more electrophilic benzylidene site of the azomethine ylid 164 and lead to the zwitterionic isonitrile adduct 166. Similarly substituted aziridines have been noted to show analogous

SCHEME XXXII

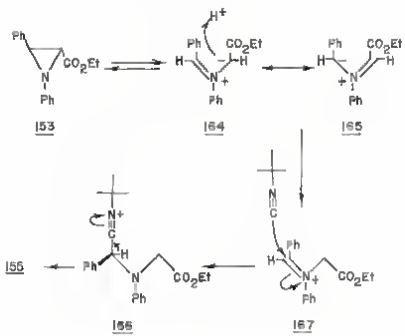
Mechanism A



behavior when thermalyzed in the presence of nucleophilic reagents.[81,82] Intramolecular proton transfer to the carbethoxymethyl anionic center[83] results in the direct formation of product 155. Mechanism A, albeit attractive, suffers from the observation that initial attempts to promote 3+1 addition by the thermolysis of aziridine 153 with excess isonitrile in the absence of a solvent resulted only in the isomerization of the aziridine. If the aziridine dipole was the sole requisite for adduct formation, mechanism A would be in agreement with experimental facts. Apparently, this is not the case. The properties of the solvent (carbon tetrachloride) must in some fashion be crucial to the overall transformation. Mechanism B accounts nicely for the catalytic activity afforded by the solvent. Proteolytic trapping of the initially formed

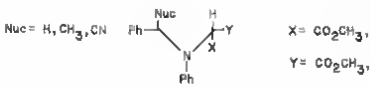
SCHEME XXXIII

Mechanism B



ylid 164 produces the aldiminium salt 167 which would be susceptible toward nucleophilic attack by the isonitrile to give 168. Loss of a proton results in betaimine 155 and regeneration of the acid catalyst.

The effects of trace amounts of acid in chlorinated solvents such as carbon tetrachloride and chloroform have been demonstrated by Gill,[84] Yun,[85] and others[86] to be responsible for heterocycles obtained from the treatment of selected Schiff bases with t-butylisonitrile 9 in these solvents. The capture of protons by azomethine ylids was shown by Carrie[82] to occur readily with functionalized aziridines of the type used in this work. And, when carried out in the presence of a variety of nucleophiles, addition products 169 were isolated in yields ranging from 30-90%.



169

The question of why 3+1 cycloaddition products between t-butylisonitrile 9 and aziridine 153 were not observed still remains puzzling. The lack of correlation between the azomethine imine and azomethine ylid systems in this respect is not immediately obvious. It is apparent that more mechanistic work needs to be done in this area.

CHAPTER IV

EXPERIMENTAL

Melting points and boiling points are recorded in degrees Centigrade and are uncorrected. Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus using 1.6-1.8 x 90 mm Kimax capillary tubes. Boiling points were determined by conventional distillation techniques or by micro capillary methods. Infrared spectra were recorded on a Perkin-Elmer Model 137 Sodium Chloride Prism spectrometer, and calibrated at 1603 cm^{-1} with a polystyrene film. Nuclear magnetic resonance spectra were recorded on a Varian Model A60-A analytical spectrometer for 60 MHz proton spectra, and a Varian Model XL-100 spectrometer for 100 MHz proton and proton decoupled spectra. Carbon-13 nuclear magnetic resonance spectra were obtained from a Varian Model XL-100 spectrometer operating at a probe frequency of 25.16 MHz. All chemical shifts (δ) in designated solvents are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Routine low resolution mass spectra, exact mass and molecular weight data were measured on an AEI MS-30 double beam spectrometer at an ionizing potential of 70 eV. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia, and in all cases are in agreement with assigned structures. Where noted, reactions and manipulations of moisture sensitive compounds were carried out in a Labconco drybox purged with a continuous stream of nitrogen. Solvent evaporations were performed at reduced pressure on a Buchi Rotavapor-R rotary evaporator equipped with a water aspirator.

t-Butylmagnesium Chloride (50)

t-Butylmagnesium chloride was prepared from t-butyl chloride and Grignard grade magnesium turnings following the procedure described by Whitmore and Rudertscher,[87] and standardized according to the method of Gilman, et al.[88]

2,2,4,4-Tetramethyl-3-Pentanone (51)

2,2,4,4-Tetramethyl-3-pentanone was prepared from t-butylmagnesium chloride and pivaloyl chloride with cuprous chloride as a catalyst according to the procedure described by Cook and Percival[34] bp 153°; ir (liquid film) 1645 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.23 (singlet)

2,2-Di-t-Butylacetyl Chloride (56)

The synthesis of 1,1-di-t-butylethanol through 2,2-di-t-butylacetyl chloride were carried out according to the methods described by Newman, Arkell and Fukunaga.[26] The product was obtained as a colorless liquid bp 83-86°/12 mm Hg; ir (liquid film) 1790 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.17 (singlet, 18H), 2.88 (singlet, 1H)

N-Ethyl-2,2-Di-t-Butylacetamide (57)

Anhydrous ethylamine (15.0 g, 0.333 mole) was placed in a 2 x 30 cm Fischer and Porter Carius tube previously cooled to 0-5° with an ice water bath. 2,2-Di-t-butylacetyl chloride (8.92 g, 46.8 mmol) was added directly to the chilled ethylamine without stirring. The Carius tube was sealed, removed from the ice water bath, shaken to effect mixing of reagents, then positioned over a magnetic stirrer where the mixture was stirred for 24 hours. The greenish product mixture was

excess ethylamine. The residue was again taken up in chloroform, washed with dilute hydrochloric acid, then dried over anhydrous magnesium sulfate. Evaporation of the solvent left a pale yellow solid. Recrystallization from hexane afforded N-ethyl-2,2-di-t-butylacetamide (7.7 g, 82%) as colorless prisms: mp 133-134°, ir (KBr) 3230 (N-H stretch) 1640 (C=O), 1545 cm^{-1} (N-H bend), nmr ($CDCl_3$) δ 1.10 (singlet, 18H), 1.13 (triplet, J=7 Hz, 3H), 1.65 (singlet, 1H), 3.23 (quartet, J=7 Hz, 2H), 5.25 (broad, 1H).

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.36; H, 12.56; N, 7.06.
Found: C, 72.33; H, 12.63; N, 7.02.

Di-t-Butylketene-N-Ethylimine (59)

A solution of N-ethyl-2,2-di-t-butylacetamide (2.00 g, 10.1 mmol) in 25 ml of benzene was prepared in a 100 ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. Phosphorus pentachloride (2.29 g, 11.0 mmol) was added and the resulting suspension refluxed for approximately 30 minutes. Benzene and phosphoryl chloride were removed by evaporation at reduced pressure, and the remaining traces of phosphoryl chloride chased with 20 ml of benzene. The crude imidoyl chloride was treated directly with triethylamine (5.57 g, 7.99 ml, 55.0 mmol) in 50 ml of benzene, and the resulting mixture refluxed for 2 hours. The precipitated triethylamine hydrochloride was removed by suction filtration and the filtrate concentrated at reduced pressure to a brown liquid. Vacuum distillation (Kugelrohr, 40-60°/0.25 mm Hg) gave di-t-butylketene-N-ethylimine (1.60 g) contaminated to the degree of approximately 25% by what appears to be 2,2-di-t-butylacetonitrile[35]: ir (liquid film) 1998 cm^{-1} (C=C=N); nmr ($CDCl_3$) δ 1.21 (singlet, 18H), 1.23 (triplet, J=7 Hz, 3H), 3.39 (quartet, J=7 Hz, 2H); m/s (calcd

for $C_{12}H_{23}N$) 181 1830. (found) 181 1827

Di-t-Butylketene-N-Ethylimidium Fluorosulfonate (60)

Freshly prepared di-t-butylketene-N-ethylimine (1 60 g) was rinsed from the Kugelrohr bulb into a 100 ml round-bottomed flask with 50 ml of anhydrous ether. The flask was then set up for magnetic stirring, and protected from atmospheric moisture with a calcium sulfate drying tube Methyl fluorosulfonate (1 51 g, 1 02 ml, 13 3 mmol) was syringed into the ketenimine solution, and the resulting mixture stirred at room temperature for approximately 30 minutes. Precipitation of the ketenimimium fluorosulfonate salt as a white flocculent suspension took place within seconds after the introduction of the methyl fluorosulfonate The colorless solid was collected on a small Büchner funnel by suction filtration and washed several times with anhydrous ether. Recrystallization from chloroform diethyl ether afforded di-t-butylketene-N-methyl-N-ethylimidium fluorosulfonate (1 50 g) as a white powder: mp 224-228° (decomp), ir (KBr) 2000 cm^{-1} (C=C=N), nmr ($CDCl_3$) δ 1.39 (singlet, 18H), 1.48 (triplet, J=7 Hz, 3H), 3.90 (singlet, 3H), 4 11 (quartet, J=7 Hz, 2H)

N-Methyl-N-Ethyl-2,2-Di-t-Butylacetamide (61)

Di-t-butylketene-N-methyl-N-ethylimidium fluorosulfonate (0 250 g, 0 847 mmol) and 15 ml of distilled water were placed in a 25 ml erlenmeyer flask The solution was made basic by adding 5 ml of 10% aqueous sodium hydroxide, and the resulting mixture stirred at room temperature for approximately 10 hours. Extraction into three 25 ml portions of diethyl ether followed by drying over anhydrous magnesium sulfate and evaporation at reduced pressure produced N-methyl-N-ethyl-

2,2-di-t-butylacetamide (0.157 g, 87%) as a pale yellow liquid. Vacuum distillation (Kugelrohr, 100-110°/0.3 mm Hg) gave an analytically pure sample as a colorless solid: mp 33.5-35.5°, ir (CCl_4) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.07 (singlet, 18H), 1.20 (triplet, J=7 Hz, 3H), 2.45 (singlet, 0.75 H), 2.49 (singlet, 0.25H), 2.83 (singlet, 0.75H), 3.0 (singlet, 2.25H), 3.39 (quartet, J=7 Hz, 2H); m/e (calcd for $C_{13}H_{27}NO$) 213.2092, (found) 213.2092.

Treatment of Di-t-Butylketone-N-Methyl-N-Ethyliminium Fluorosulfonate (60) with Sodium Bis(trimethylsilyl)amide: N,N'-Diethyl-2,5-Bis(2,2,4,4-tetramethyl-3-pentylidene)piperazine (63)

In a drybox, di-t-butylketone-N-methyl-N-ethyliminium fluorosulfonate (0.638 g, 2.16 mmol), sodium bis(trimethylsilyl)amide (0.595 g, 3.25 mmol), and 25 ml of dry benzene were placed in 100 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. The resulting heterogeneous slurry was stirred at room temperature under nitrogen atmosphere for a period of 28 hours. During this time, the mixture became somewhat more homogeneous and assumed a bright yellow appearance. The fluorosulfonate salts and excess silylamide base were removed by suction filtration through a bed of Celite, and the clear yellow filtrate evaporated at reduced pressure to a yellow oil (0.406 g). Crystallization from ethyl acetate produced colorless flakes of N,N'-diethyl-2,5-bis(2,2,4,4-tetramethyl-3-pentylidene) piperazine in two crops (0.2182 g, 52%); mp 154-156°; ir ($CHCl_3$) 1600 cm^{-1} (C=C=N); nmr 60 MHz ($CDCl_3$) δ 1.07 (triplet, J=7 Hz, 6H), 1.30 (singlet, 9H), 1.43 (singlet, 9H), 2.33 3.58 (multiplet, 8H), nmr 100 MHz ($CDCl_3$) δ 1.07 (triplet, J=7 Hz, 6H), 1.31 (singlet, 9H), 1.43 (singlet, 9H), 2.60 (doublet, J_{AB}=10 Hz, 2H, endocyclic CH_2),

2.74 (doublet of quartets, $J_{A',B'}$=11.5 Hz, J_{H,CH_3}=7 Hz, 2H, exocyclic CH_2), 3.01 (doublet of quartets, $J_{A',B'}$=11.5 Hz, J_{H,CH_3}=7 Hz, 2H, exocyclic CH_2), 3.35 (doublet, J_{AB}=10 Hz, 2H, endocyclic CH_2), nmr ^{13}C ($CDCl_3$) δ 13.0 (quartet, CH_3CH_3), 33.8 (quartet, t-butyl), 42.5 (triplet, exocyclic CH_2), 45.2 (triplet, endocyclic CH_2), 141.3 (singlet, exocyclic, C=C), 147.1 (singlet, endocyclic, C=C), m/e (calcd for $C_{26}H_{50}N_2$) 390.3973, (found) 390.3977.

Treatment of Di-t-Butylketone N-Methyl-N-Ethylimidium Fluorosulfonate (60) with Sodium Bis(trimethylsilyl)amide in Refluxing Benzene

In a drybox, di-t-butylketone-N-ethylimidium fluorosulfonate (0.500 g, 1.69 mmol), sodium bis(trimethylsilyl)amide (0.466 g, 2.54 mmol), and 20 ml of dry benzene were combined in a 100 ml round-bottomed flask containing a small magnetic stirring bar. The flask was removed from the drybox, positioned over a magnetic stirrer and equipped with a reflux condenser and a nitrogen atmosphere. The reaction mixture was refluxed for 6.5 hours before being filtered through a small Büchner funnel containing a bed of Celite. The yellow filtrate was evaporated to an oil (0.4044 g), diluted with approximately 8 ml of ethyl acetate, and placed in a refrigerator freezer. After several hours, crystalline flakes of piperazine dimer (0.197 g, 59.7%, mp 154-156°) appeared and were collected by suction filtration. The mother liquor was examined spectroscopically and was found by comparison with an authentic sample to contain mostly N-methyl-N-ethyl-2,2-di-t-butylacetamide.

Treatment of Di-t-Butylketene-N-Methyl-N-Ethylisinium Fluorosulfonate (60) with Bis(trimethylsilyl)amide in Hexamethylphosphoramide (HMPA)

A solution of sodium bis(trimethylsilyl)amide (0.448 g, 2.44 mmol) in 50 ml of dry hexamethylphosphoramide was prepared in a 50 ml round-bottomed flask equipped with a magnetic stirring bar and a rubber septum. A solution of di-t-butylketene-N-methyl-N-ethylisinium fluorosulfonate (0.482 g, 1.63 mmol) in 5 ml of dry hexamethylphosphoramide was syringed into the stirred base in one portion. The resulting homogeneous mixture was stirred at room temperature for 12 hours. The mixture was diluted with 50 ml of water, then extracted into two 50 ml portions of diethyl ether. The ether extracts were combined, concentrated at reduced pressure, and vacuum distilled (Kugelrohr) to remove the remaining hexamethylphosphoramide. The pot residue was taken up in ethylacetate, which, after several hours of refrigeration, produced piperazine dimer (0.0672 g) in 21% yield.

The distillate was taken up in 20 ml of diethyl ether, washed three times with 25 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a pale yellow liquid (0.1802 g). This material showed major nmr signals at δ 1.07 (singlet, 18H), 1.20 (triplet, J=7 Hz, 3H), 2.45 (singlet, 0.75H), 3.0 (singlet, 2.25H), and 3.39 (quartet, J=7 Hz, 2H) and was shown by comparison with an authentic sample to be N-methyl-N-ethyl-2,2-di-t-butylacetamide (52%).

Exo-N-Ethyl-1-(2,2,4,4-Tetramethyl-3-Pentylidene)perhydro-4,7-Methanoisoindole (66), and Exo-N-Ethyl-1-(2,2,4,4-Tetramethyl-3-Pentyl)-3a,4,5,6,7,7a-Hexahydro-4,7-Methano-3H-Isoindolinium Chloride (67)

Di-t-butylketone-N-methyl-N-ethyliminium fluorosulfonate (0.400 g, 1.36 mmol), norbornene (1.28 g, 13.6 mmol), and 15 ml of dry benzene were combined in a 50 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. The flask was transferred to a drybox and positioned over a magnetic stirrer where sodium bis(trimethylsilyl)amide (0.75 g, 4.09 mmol) was added. The resulting suspension was then stirred at room temperature under nitrogen atmosphere for 23 hours. The golden reaction mixture was passed through a filter funnel containing a bed of Celite, and the yellow filtrate evaporated at reduced pressure to remove solvent and excess norbornene. After removing the residual traces of solvent by evaporation at high vacuum, exo-N-ethyl-1-(2,2,4,4-tetramethyl-3-pentylidene)perhydro-4,7-methanoisoindole (0.386 g, 98.5%) was obtained as an acid sensitive, pale yellow oil: ir ($CHCl_3$) 1625 cm^{-1} (C=C-N); nmr ($CDCl_3$) δ 1.00 (triplet, J=7 Hz, methyl), 1.35 (singlet, t-butyl), 1.50 (singlet, t-butyl), 1.0-3.0 (multiplet, methylene and norbornyl); ^{13}C nmr ($CDCl_3$) δ 16.0 (quartet, $-CH_2-\underline{C}H_3$), 26.2 (triplet, C_5), 31.1 (quartet, t-butyl), 31.6 (triplet, C_6), 32.6 (quartet, t-butyl), 33.6 (singlet, t-butyl), 36.0 (singlet, t-butyl), 36.7 (doublet, C_4), 41.1 (doublet, C_7), 41.8 (triplet, C_8), 44.3 (triplet, $-\underline{C}H_2-CH_3$), 51.1 (doublet, C_{3a}), 54.6 (doublet, C_{7a}), 57.4 (triplet, C_3), 124.8 (singlet, exocyclic C=C), 141.6 (singlet, endocyclic C=C), m/e (<u>calcd</u> for $C_{21}H_{35}N$) 289.2769, (<u>found</u>) 289.2761.

The crude isoindole, was diluted with approximately 5 ml of benzene and applied to a neutral alumina column (1.25 x 10 cm) packed in petroleum ether (65-110°). Five 40 ml fractions were collected with

chloroform and discarded. A sixth and final 40 ml fraction was obtained with anhydrous methanol, evaporated to a golden oil, then diluted with ethyl acetate which produced colorless platelets of exo-N-ethyl-1-(2,2,4,4-tetramethyl-3-pentyl)-3a,4,5,6,7,7a-hexahydro-4,7-methano-3H-isoindolinium chloride (0.289 g, 65.3%); mp 176-179° (decomp.), ir ($CHCl_3$) 1620 cm^{-1} (C=N), nmr ($CDCl_3$) δ 1.25 (singlet, 9H), 1.28 (singlet, 9H), 1.50-1.80 (broad multiplet, 6H, H_5, H_6, H_8), 1.53 (triplet, J=7 Hz, 3H), 2.50 (broad singlet, 1H, H_7), 3.00 (singlet, 1H, exocyclic-CH), 3.43 (broad doublet, $J_{3a,7a}$=8 Hz, 1H, H_{7a}), 4.08-5.18 (multiplet, 4H, endocyclic and exocyclic CH_2); ^{13}C nmr ($CDCl_3$) δ 13.0 (quartet, $-CH_2-\underline{C}H_3$), 27.2 (triplet, C_6), 29.5 (triplet, C_5), 31.8 (quartet, t-butyl), 32.7 (quartet, t-butyl), 36.8 (singlet, t-butyl), 40.3 (doublet, C_4), 40.7 (doublet, C_7), 42.8 (doublet, C_{3a}), 47.9 (triplet, $-\underline{C}H_2CH_3$), 59.9 (doublet, exocyclic-CH), 60.2 (doublet, C_{7a}), 64.5 (triplet, C_3), 195.2 (singlet, C_1), m/e (calcd for $C_{20}H_{35}N$) 289.2769, (found) 289.2763;

Anal. Calcd for $C_{20}H_{35}N \cdot HCl \cdot H_2O$ C, 69.82, H, 11.14, N, 4.07;
Found: C, 69.84, H, 11.15, N, 4.07.

Exo N-Ethyl-1-(2,2,4,4-Tetramethyl-3-Pentyl)-6(7)-Methyl-3a,4,9,9a-Tetrahydro-4,9-Methano-3H-Benz[f]isoindolinium Chloride (69, 69')

Di-t-butylketene-N-methyl-N-ethyliminium fluorosulfonate (0.7773 g, 2.634 mmol), and 10 ml of dry benzene were combined in a 50 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. The flask was transferred to a drybox, positioned over a magnetic stirrer and sodium bis(trimethylsilyl)amide (0.996 g, 5.27 mmol) was added. The resulting suspension was then stirred at room temperature under nitrogen atmosphere for 27 hours

The golden reaction mixture was passed through a filter funnel containing a bed of Celite. The pale yellow filtrate was evaporated at reduced pressure to remove solvent and some 4-methylbenzonorbornadiene. The residue was diluted with approximately 5 ml of benzene and applied to an alumina column (2.5 x 12 cm) packed in benzene. Seven 40 ml fractions were collected with methylene chloride and evaporated to oils. These were all shown by spectroscopic comparison with an authentic sample to be 5-methylbenzonorbornadiene. An eighth and final fraction was obtained with 80 ml of anhydrous methanol. This was evaporated to a yellow oil, then diluted with hot ethyl acetate. Upon cooling, exo-N-ethyl-1-(2,2,4,4-tetramethyl-3-pentyl)-b(7)-methyl-3a,4,9,9a-tetrahydro-4,9-methano-3H-benz[f]isoindolinium chloride (0.176 g, 17.4%) was obtained as a colorless crystalline solid: mp 252-253°, ir ($CHCl_3$) 1610 cm^{-1} (C=N), nmr ($CDCl_3$) δ 1.20 (singlet, 9H), 1.35 (singlet 9H), 1.56 (multiplet- 3H, $-CH_2\underline{CH_3}$) 2.00 (broad singlet, 2H, H_{10}), 2.32 (singlet, 3H), 2.79 (broad doublet, $J_{3a,9a}$=8 Hz, 1H, H_{3a}), 2.98 (singlet, 1H, exocyclic CH), 3.44 (broad doublet, $J_{3a,9a}$=8 Hz, 1H, H_{9a}), 3.57 (broad singlet, 1H, H_4), 3.92 (broad singlet, 1H, H_9), 4.17-5.18 (multiplet, 4H, endocyclic and exocyclic CH_2), 6.75-7.20 (multiplet, 3H, aromatic); ^{13}C nmr ($CDCl_3$) δ 13.0 (quartet, $-CH_2-\underline{CH_3}$), 21.5 (quartet, b-CH_3, 7-CH_3*), 31.7 (quartet, $\underline{CH_3}$, t-butyl), 32.8 (quartet, $\underline{CH_3}$, t-butyl), 36.8 (singlet, $\underline{C}$, t-butyl), 36.9 (singlet, C, t-butyl), 40.5 (doublet, C_{3a}), 40.6 (doublet, C_{3a}*), 43.7 (triplet, C_{10}), 47.3 (doublet, C_4), 47.7 (doublet, C_4*), 48.4 (triplet, $\underline{CH_2}CH_3$), 49.5 (doublet, C_9), 49.8 (doublet, C_9*), 60.3 (doublet, $\underline{CH}$, exocyclic), 60.9 (doublet, C_{9a}), 61.1 (doublet, C_{9a}*), 62.6 (triplet, C_3), 120.7 (doublet, C_7), 121.8 (doublet, C_6*), 122.0 (doublet, C_8), 123.2 (doublet, C_5*), 127.5 (doublet, C_5), 128.1

(doublet, C_5*), 136.9 (singlet, C_6), 137.7 (singlet, C_7*), 142.5 (singlet, C_{4a}), 143.6 (singlet, C_{4a}*), 145.6 (singlet, C_{8a}*), 146.7 (singlet, C_{8a}), 183.7 (singlet, C_1); (calcd for $C_{25}H_{37}N$) 351.2925, (found) 351.2927.

2,2-Diphenylacetyl Chloride

2,2-Diphenylacetic acid (28.0 g, 0.132 mole) and thionyl chloride (47.1 g, 28.5 ml, 0.396 mole) were combined in a 250 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The slurry was refluxed by 4.5 hours, during which time the mixture became homogeneous and developed a yellow appearance. The excess thionyl chloride was removed by evaporation at reduced pressure and the residue vacuum distilled at 123°/0.1 mm Hg (lit.[89] bp 170-1°/16 mm Hg). 2,2-Diphenylacetyl chloride (29.7 g, 97.5%) was obtained as a yellow orange liquid which solidified on standing. Ir (CCl_4) 1975 cm^{-1} (C=O); nmr (CCl_4) δ 5.33 (singlet, 1H), 7.20 (singlet, 10H).

N-Phenyl-2,2-Diphenylacetamide (82)

A solution consisting of aniline (12.6 g, 0.135 mole), triethylamine (13.6 g, 196. ml, 0.135 mole) and 300 ml of benzene was prepared in a 1000 ml three-necked round-bottomed flask equipped with an addition funnel, mechanical stirrer, and an ice water cooling bath. 2,2-Diphenylacetyl chloride (28.2 g, 0.129 mole) in 100 ml of benzene was added dropwise to the above amine solution and the mixture stirred for approximately 10 hours. The triethylamine hydrochloride was collected by suction filtration and washed several times with 10%

*Denotes signals thought to be due to minor (7)-CH_3 isomer.

sodium hydroxide. The odorless solid which remained was collected and saved. The benzene filtrate was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate and evaporated to give a second crop of colorless solid. The two crops were combined and recrystallized from benzene-petroleum ether (65-110°). N-Phenyl-2,2-diphenylacetamide (26.0 g, 70%) was collected as a fluffy colorless solid mp 179.5-180.5° (lit.[30] mp 180°); ir (KBr) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.05 (singlet, 1H), 6.92-7.55 (multiplet, 15H).

Diphenylketene-N-Phenylimine (83)

Diphenylketene-N-phenylimine was prepared by sodium iodide dechlorination of the α-chloroimidoyl chloride precursor according to the procedure described by Stevens and French[31] mp 53-55° (lit.[31] mp 55-56°), ir (liquid film) 1998 cm^{-1} (C=C=N), nmr (CCl_4) δ 6.95-7.43 (multiplet).

Alkylation of Diphenylketene-N-Phenylimine (83)

A solution of diphenylketene-N-phenylimine (1.50 g, 5.30 mmol), and 25 ml of anhydrous ether was prepared in a 50 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. This solution was treated with methyl fluorosulfonate (0.525 ml, 0.741 g, 6.50 mmol) and stirred at room temperature for a period of 48 hours. The clay colored quinazolinium salt (1.50 g, 83%) was collected in a small Buchner funnel and washed several times with ether to remove excess methyl fluorosulfonate and minor by-products. Purification was achieved by dissolving the crude fluorosulfonate salt in a minimum amount of hot chloroform and diluting with approximately

100 ml of hexane. The resulting solution produced brownish granules of 1-methyl-2-benzhydryl-3-phenyl-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate after several hours of refrigeration: mp 282-284° (decomp.); nmr (trifluoroacetic acid) δ 3.38 (singlet, 3H), δ 1 (singlet, 1H), 6.4-7.7 (multiplet, 29H)

1-Methyl-3-Phenyl-2,4-Dibenzhydrylidene-1,2,3,4-Tetrahydroquinazoline (85)

1-Methyl-2-benzhydryl-3-phenyl-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate (4.00 g, 6.13 mmol), 75 ml of 1,4-dioxane, and 20 ml of 20% sodium carbonate were combined in a 125 ml erlenmeyer flask and stirred magnetically until a clear yellow solution remained (ca. 30 minutes). The product mixture was placed on a rotary evaporator where most of the water and dioxane were removed at reduced pressure. The pasty yellow residue which remained was taken up in chloroform, dried over anhydrous magnesium sulfate, then evaporated to dryness. Recrystallization from petroleum ether (65-110°) produced 1-methyl-3-phenyl-2,4-dibenzhydrylidene-1,2,3,4-tetrahydroquinazoline (3.3 g, 95%) as a fluorescent yellow solid: mp 244-246.5°; nmr (CCl_4) δ 2.68 (singlet, 3H), 6.0-7.25 (multiplet, 29H), m/e (calcd for $C_{41}H_{32}N_2$) 552.2564, (found) 552.2581.

1-Methyl-2-Benzhydryl-3-Phenyl-4-Benzhydrylidene-1,2,3,4-Tetrahydroquinazoline (86)

1-Methyl-2-benzhydryl-3-phenyl-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate (1.05 g, 1.61 mmol) and 25 ml of ethanol were combined in a 50 ml erlenmeyer flask equipped with a magnetic stirring bar. Sodium borohydride (0.15 g, 3.96 mmol) was added in several small increments to the stirred malt solution. After the

vigorous reaction subsided, the mixture was stirred at room temperature for 30 minutes, then quenched with 50 ml of water. The precipitated orange solid was extracted into two 50 ml portions of ether, dried over anhydrous magnesium sulfate, and evaporated to dryness. 1-Methyl-2-benzhydryl-3-phenyl-4-benzhydrylidene-1,2,3,4-tetrahydroquinazoline (0.84 g, 94%) was obtained as a yellow orange solid which could be recrystallized from hot isopropanol. The orange crystals, however, were found to be heavily occluded with solvent. An analytical sample was prepared by repeated chasings with chloroform followed by drying under high vacuum. mp 142-155° (decomp.); nmr ($CDCl_3$) δ 2.16 (singlet, 3H), 4.93 (quartet, J_{AB}=11 Hz, 2H, δ_A=5.13, δ_B=4.73), 6.1-7.5 (multiplet, 29H); m/e (<u>calcd</u> for $C_{41}H_{34}N_2$) 554.2720, (<u>found</u>) 554.2720.

<u>Acid Hydrolysis of 1-Methyl-2-Benzhydryl-3-Phenyl-4-Benzhydrylidene-1,2,3,4-Tetrahydroquinazoline (85)</u>

1-Methyl-2-benzhydryl-3-phenyl-4-benzhydrylidene-1,2,3,4-tetrahydroquinazoline (0.5445 g, 0.9828 mmol), and 40 ml of concentrated hydrochloric acid were placed in a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The suspension was stirred under reflux for 24 hours, then cooled to ambient temperature. The material clinging to the inner walls of the condenser was rinsed into the reaction mixture with methylene chloride. The pot mixture was extracted into three 25 ml portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate, then evaporated at reduced pressure to an oily residue (0.4859 g)

Neutralization of the aqueous acid layer with 10% sodium hydroxide followed by extraction into ether, drying over anhydrous magnesium sulfate and evaporation at reduced pressure, produced 0.0877 g (96%) aniline.*

Crystallization of the organic residue from hot 95% ethanol produced 1,1-diphenyl-2-(4-N-methylamino-3-diphenylacetylphenyl) ethylene (0.1141 g, 24%) as fine lemon yellow needles: mp 162.5-164°. ir ($CHCl_3$) 3300 (N-H), 1635 cm^{-1} (C=O), nmr ($CDCl_3$) δ 2.8 (doublet, J=5 Hz, 3H, collapses to a singlet with D_2O), 5.41 (singlet, 1H), 6.43 (doublet, $J_{5,6}$=8.5 Hz, 1H, H_5), 6.72 (singlet, 1H), 6.8-7.4 (multiplet, 2H), 7.57 (doublet, $J_{2,6}$=2.0 Hz, 1H, H_2), 8.88 (broad, 1H, washes out with D_2O), m/e (<u>calcd</u> for $C_{35}H_{29}NO$) 479.2248, (<u>found</u>) 479.2252.

The filtrate from the above crystallization was concentrated at reduced pressure and applied to a silica gel column packed in carbon tetrachloride. The first fraction (eluted with 40 ml of carbon tetrachloride) contained an unidentified material and was discarded. A second fraction was collected with 80 ml of methylene chloride: carbon tetrachloride (25:75), and evaporated at reduced pressure to a yellow oil (0.2757 g). Spectroscopic (nmr) analysis of this component indicated the presence of N-methyl-2-diphenylacetylaniline (0.2230 g, 75%). An analytical sample was prepared by vacuum distillation (Kugelrohr) at 170-175°/0.2 mm Hg. ir ($CHCl_3$) 3200 (N-H), 1625 cm^{-1} (C=O), nmr (CCl_4) δ 2.89 (doublet, J=5 Hz, 3H, collapses to a singlet with D_2O), 5.93 (singlet, 1H), 6.22-6.63 (multiplet, 2H, H_4, H_6), 6.94-7.34 (multiplet, 11H), 7.68 (multiplet, $J_{3,4}$=8 Hz, $J_{3,5}$=1.5 Hz, 1H, H_3), 8.86 (broad, 1H, washes out with D_2O), m/e (<u>calcd</u> for $C_{21}H_{19}NO$) 301.1466, (<u>found</u>) 301.1459.

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* Identification was based on spectroscopic comparison with an authentic sample.

N-(p-Tolyl)-2,2-Diphenylacetamide (91)

A solution consisting of p-toluidine (12.3 g, 0.115 mole), triethylamine (11.6 g, 16.0 ml, 0.115 mole), and 400 ml of benzene was prepared in a 1000 ml three-necked round-bottomed flask equipped with an addition funnel, mechanical stirrer, and an ice water cooling bath. 2,2-Diphenylacetyl chloride (26.0 g, 0.113 mole) in 100 ml of benzene was added dropwise to the above amine solution and stirred for 3 hours. The triethylamine hydrochloride was collected by suction filtration and washed several times with 10% aqueous sodium hydroxide. The colorless solid which remained was collected and saved. The benzene filtrate was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate then evaporated to a second crop of product. The two crops were combined and recrystallized from benzene-petroleum ether. N-(p-Tolyl)-2,2-diphenylacetamide (26.0 g, 77%) was obtained as a colorless solid: mp 171-172.5° (lit.[91] mp 172-173°), ir ($CHCl_3$) 1675 cm^{-1} (C=O), nmr ($CDCl_3$) δ 2.25 (singlet, 3H), 5.02 (singlet, 1H), 6.80-7.72 (multiplet, 15H)

Diphenylketene-N-(p-Tolyl)imine (92).

Diphenylketene-N-(p-tolyl)imine was prepared by the direct dehydration of the corresponding amide according to the method described by Stevens and Singhal[31] mp 81.5-83.5° (lit.[31] mp 82-84°); ir (liquid film) 2000 cm^{-1} (C=C=N); nmr ($CDCl_3$) δ 2.32 (singlet, 3H), 6.92-7.42 (multiplet, 14H).

Alkylation of Diphenylketene-N-(p-Tolyl)imine (92)

A solution of diphenylketene-N-(p-tolyl)imine (4.50 g, 16.0 mmol) and 75 ml of anhydrous ether was prepared in a 250 ml round-bottomed

flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. This solution was treated with methyl fluorosulfonate (2.60 ml, 3.50 g, 32.0 mmol) and stirred at room temperature for 48 hours. Precipitation of the crude quinazolinium salt occurred suddenly after the first 24 hours of stirring (in some instances, seeding or scratching with a glass rod were necessary to induce crystallization). The too colored 1,6-dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate (4.60 g, 84%) was collected in a small Buchner funnel and washed several times with anhydrous ether to remove excess methyl fluorosulfonate and minor by-products. Purification via crystallization was achieved by the addition of 125-150 ml of hot benzene to a solution of the crude quinazolinium salt in 20-25 ml of chloroform. Tan platelets of 1,6-dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate appeared on cooling: mp 240-248° (decomp.); nmr (trifluoroacetic acid) δ 2.15 (singlet, 3H), 2.32 (singlet, 3H), 3.31 (singlet, 3H), 6.1 (singlet, 1H), 6.38-7.68 (multiplet, 27H)

1,6-Dimethyl-3-(p-Tolyl)-2,4-Dibenzhydrylidene-1,2,3,4-Tetrahydroquinazoline (94)

1,6-Dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate (4.00 g, 5.84 mmol), 75 ml of 1,4-dioxane, and 20 ml of 10% sodium hydroxide were combined in a 125 ml erlenmeyer flask and heated on a steam bath for 30 minutes with intermittent swirling. The product mixture was placed on a rotary evaporator where most of the water and dioxane were removed at reduced pressure. The pasty yellow residue which remained was taken up in chloroform, dried over anhydrous magnesium sulfate, then evaporated

to dryness. Recrystallization from petroleum ether (65-110°) produced 1,6-dimethyl-3-(p-tolyl)-2,4-di-benzhydrylidene-1,2,3,4-tetrahydroquinazoline (3.35 g, 98%) as a fluorescent yellow solid mp 260-261.5°, nmr ($CDCl_3$) δ 1.84 (singlet, 3H), 2.25 (singlet, 3H), 2.67 (singlet, 3H), 6.19 (doublet, $J_{7,8}$=8 Hz, 1H, H_8), 6.36 (doublet, $J_{5,7}$=2 Hz, 1H, H_5), 6.56-7.28 (multiplet, 25H); m/e (calcd for $C_{43}H_{36}N_2$) 580.2876, (found) 580.2857

1,6-Dimethyl-2-Benzhydryl-3-(p-Tolyl)-4-Benzhydrylidene 1,2,3,4-Tetrahydroquinazoline (95)

1,6-Dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-3,4-dihydroquinazolinium fluorosulfonate (1.40 g, 2.04 mmol), and 50 ml of ethanol were combined in a 125 ml erlenmeyer flask equipped with a magnetic stirring bar. Sodium borohydride (0.30 g, 7.92 mmol) was added in several small increments to the stirred salt solution. After the initial vigorous reaction subsided, the mixture was stirred at room temperature for 30 minutes, then quenched with 50 ml of water. The precipitated yellow orange solid was extracted into two 60 ml portions of ether, dried over anhydrous magnesium sulfate, and evaporated to dryness. 1,6-Dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-1,2,3,4-tetrahydroquinazoline (1.15 g, 96%) was obtained, and recrystallized from isopropanol/water. The orange granules, however, were found to be heavily occluded with isopropanol. An analytical sample was afforded by repeated chasings with chloroform followed by drying under high vacuum: mp 108-150° (decomp.), nmr ($CDCl_3$) δ 1.92 (singlet, 3H), 2.18 (singlet, 6H), 4.86 (quartet, J_{AB}=11 Hz, 2H, δ_A=5.06, δ_B=4.66), 6.16-7.47 (multiplet, 27H), m/e (calcd for $C_{43}H_{38}N_2$) 582.3034, (found) 582.3050.

Acid Hydrolysis of 1,6-Dimethyl-2-Benzhydryl-3-(p-Tolyl)-4-Benzhydrylidene-1,2,3,4-Tetrahydroquinazoline (95)

1,6-Dimethyl-2-benzhydryl-3-(p-tolyl)-4-benzhydrylidene-1,2,3,4-tetrahydroquinazoline (1.00 g, 1.72 mmol), and 90 ml of concentrated hydrochloric acid were combined in a 200 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The bright cherry red solution was stirred under reflux for 36 hours. During this time, the color faded to a pale orange. After cooling to room temperature, the material clinging to the inner walls of the condenser was rinsed into a separate vessel with chloroform and evaporated at reduced pressure to a colorless liquid. This material (0.130 g) was shown to contain mostly diphenylacetaldehyde.* The pot mixture was transferred to a separatory funnel where the organic soluble components were extracted into two 50 ml portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate, then evaporated at reduced pressure to a yellow oil (0.4985 g). This material was applied to an alumina column packed in petroleum ether 65-110°, and eluted with the same solvent. A singlet yellow band was collected in the second fraction, concentrated to approximately 10 ml, then placed in a refrigerator freezer where fine yellow needles of N-methyl-2-diphenylacetyl-p-toluidine (0.169 g, 31%) appeared after several hours: mp 132-133 5°; ir (KBr) 3240 (N-H), 1628 cm^{-1} (C=O), nmr ($CDCl_3$) δ 2.18 (singlet, 3H), 2.88 (doublet, J=3 Hz, 3H, collapses to a singlet with D_2O), 4.13 (singlet, 1H), 6.62 (doublet, $J_{5,6}$=9 Hz, 1H, H_6), 7.07-7.40 (multiplet, 11H), 7.66 (doublet, $J_{3,5}$=2 Hz, 1H, H_3), 8.75 (broad, 1H, washes out with D_2O); m/e (<u>could</u> for $C_{22}H_{21}NO$) 315.1623, (<u>found</u>) 315.1646

Neutralization of the aqueous acid layer with 10% sodium hydroxide followed by extraction into ether, drying over anhydrous magnesium

sulfate, and evaporation to dryness, afforded p-toluidine* (0.182 g, 99%).

Isobutyryl Chloride (136)

Isobutyric acid (220.0 g, 2.50 moles) and thionyl chloride (202.1 g, 122 ml, 1.70 moles) were combined in a 500 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. After the initial endothermic reaction had ceased, the mixture was gently refluxed for 6 hours. The reflux condenser was replaced by a fractionating column and the component distilling at 90-93° was collected. Isobutyryl chloride (146.7 g, 98%) was obtained as a pungent, colorless liquid: ir (liquid film) 1800 cm^{-1} (C=O); nmr (neat) δ 1.2° (doublet, J=7 Hz, 6H), 2.97 (heptet, J=7 Hz, 1H).

N-Phenylisobutyramide (99)

A solution consisting of aniline (46.6 g, 0.500 mole) triethylamine (50.6 g, 72.7 ml, 0.500 mole), and 500 ml of chloroform was prepared in a 100 ml three-necked round-bottomed flask equipped with an addition funnel, mechanical stirrer, and an ice water cooling bath. Isobutyryl chloride (45.0 g, 0.422 mole) in 200 ml of chloroform was added dropwise to the above amine solution, then stirred at ambient temperature for 12 hours. The chloroform mixture was washed with dilute hydrochloric acid, 20% sodium carbonate, and, finally, with water. The organic layer was dried over anhydrous magnesium sulfate then evaporated to dryness. Recrystallization of the residue from

* Identification was based on spectroscopic comparison with an authentic sample.

petroleum ether (65-110°) afforded N-phenylisobutyramide (57.0 g, 83%) as a colorless crystalline solid: mp 105.5-107° (lit.[89] mp 106-107°), ir ($CHCl_3$) 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.20 (doublet, J=7 Hz, 6H), 2.53 (heptet, J=7 Hz, 1H), 6.87-7.62 (multiplet, 5H), 7.87 (broad, 1H).

Dimethylketene-N-Phenylimine (29)

N-Phenylisobutyramide (20.0 g, 0.122 mole) and 100 ml of benzene were combined in a 200 ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. Phosphorus pentachloride (25.5 g, 0.123 mole) was added to the amide slurry and the mixture stirred under reflux for 2 hours. Evaporation of the benzene and phosphoryl chloride at reduced pressure left an oily residue which, when vacuum distilled at 81°/2.3 mm Hg, afforded N-phenylliminoisobutyryl chloride (18.5 g, 83%); ir (liquid film) 1690 cm^{-1} (C=N); nmr (CCl_4) δ 1.11 (doublet, J=7 Hz, 6H), 2.87 (heptet, J=7 Hz, 1H), 6.60-7.42 (multiplet, 5H). The imidoyl chloride (12.2 g, 0.0671 mole), 200 ml of toluene, and triethylamine (67.8 g, 97.4 ml, 0.670 mole) were added consecutively to a 500 ml round-bottomed flask equipped with a Friedrichs condenser, magnetic stirring bar, and a calcium sulfate drying tube. After stirring under reflux for 9 hours, the brown product mixture was cooled to room temperature, filtered, and concentrated at reduced pressure to a brown liquid. Vacuum distillation at 73°/2.8 mm Hg (lit.[92] bp 98-100°/12 mm Hg) produced dimethylketene-N-phenylimine (6.0 g, 63%) as a greenish yellow liquid: ir (liquid film) 2000 cm^{-1} (C=C=N); nmr (CCl_4) δ 1.73 (singlet, 6H), 7.17 (multiplet, 5H).

1,3,5-Triphenyl-2,4,6-triisopropylidenehexahydro-s-triazine (101)

A solution of dimethylketone-N-phenylimine (3.00 g, 21.0 mmol) in 100 ml of anhydrous ether was prepared in a 250 ml round-bottomed flask equipped with a magnetic stirring bar, and chilled to 0-5° with an ice water bath. This solution was treated with methyl fluorosulfonate (1.67 ml, 2.35 g, 21.0 mmol), then stirred at ambient temperature for 24 hours. The ethereal solution was decanted from the small amount of brown oil (0.50 g) adhering to the walls of the flask and evaporated at reduced pressure to a colorless crystalline solid (2.30 g). The crude triazine was crystallized from hot absolute ethanol to yield 1,3,5-triphenyl-2,4,6-triisopropylidenehexahydro-s-triazine (2.20 g, 73%) as colorless prisms, mp 166-167° (lit.[65] Mp 163-164°), ir ($CHCl_3$) 1675 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 1.43 (singlet, 18H), δ 6.53-7.33 (multiplet, 15H), m/e (calcd for $C_{31}H_{33}N_3$) 435.2674, (found) 435.2655.

Acid Catalyzed Cyclization of Dimethylketone-N-Phenylimine (29) to 1,3,5-Triphenyl-2,4,6-Triisopropylidenehexahydro-s-Triazine (101)

Dimethylketone-N-phenylimine (0.50 g, 3.4 mmol) and 25 ml of anhydrous ether were combined in a 50 ml round-bottomed flask and stirred magnetically until dissolved. A singlet drop of fluorosulfonic acid was added to this solution and the resulting mixture stirred at ambient temperature for 14 hours. Evaporation of the ether at reduced pressure left a pale yellow solid residue. Recrystallization from absolute ethanol afforded colorless crystals (0.30 g, 60%, mp 166-167°). Spectroscopic comparison with that of an authentic sample identified this material as 1,3,5-triphenyl-2,4,6-triisopropylidenehexahydro-s-triazine.

1,3,5-Triphenyl-2-isopropyl-4,6-Diisopropylidene-3,4,5,6-Tetrahydro-s-Triazinium Fluorosulfonate (103)

A solution of dimethylketene-N-phenylimine (3.00 g, 21.0 mmol) in 100 ml of anhydrous ether was prepared in a 250 ml round-bottomed flask equipped with a magnetic stirring bar. Methyl fluorosulfonate (4.70 g, 3.34 ml, 41.2 mmol) was introduced via a syringe and the resulting mixture stirred at room temperature for 24 hours. The ethereal product mixture was decanted into a 250 ml erlenmeyer flask and covered loosely with a Kimwipe. After 24 hours of standing, the yellow crystals of 1,3,5-triphenyl-2-isopropyl-4,6-diisopropylidene-3,4,5,6-tetrahydro-s-triazinium fluorosulfonate (2.50 g, 85%) were collected and recrystallized from chloroform carbon tetrachloride: mp 200-203° (decomp.); ir (KBr) 1640 cm^{-1} (C=C-N); nmr (trifluoroacetic acid) δ 0.74 (doublet, J=7 Hz, 6H), 1.38 (singlet, 6H), 2.06 (singlet, 6H), 2.98 (multiplet, J=7 Hz, 1H), 7.17-7.85 (multiplet, 15H).

Protonation of 1,3,5-Triphenyl-2,4-Triisopropylidenehexahydro-s-Triazine (101) with Chlorosulfonic Acid

Chlorosulfonic acid (0.150 g, 1.29 mmol) and 40 ml of carbon tetrachloride were combined in a 100 ml round-bottomed flask equipped with a magnetic stirring bar and an addition funnel, then chilled to 0-5° with an ice water bath. 1,3,5-Triphenyl-2,4,6-triisopropylidenehexahydro-s-triazine (0.500 g, 1.15 mmol) in 40 ml of carbon tetrachloride was added in a steady stream to the stirred acid solution. A yellow solid precipitated immediately. Filtration and recrystallization of this solid from chloroform:carbon tetrachloride produced 1,3,5-triphenyl-2-isopropyl-4,6-diisopropylidene-3,4,5,6-tetrahydro-s-triazinium chlorosulfonate (0.16 g, 26%) as yellow prisms: mp 244-245° (decomp.), nmr (trifluoroacetic acid) δ 0.78 (doublet, J=7 Hz, 6H),

1.43 (singlet, 6H), 2.08 (singlet, 6H), 2.68-3.35 (heptet, J 7 Hz, 1H), 7.22-8.48 (multiplet, 15H)

Attempted Hydrolysis of 1,3,5-Triphenyl-2-Isopropyl-4,6-Diisopropylidene-3,4,5,6-Tetrahydro-s-Triazinium Fluorosulfonate (103)

1,3,5-Triphenyl-2-isopropyl-4,6-diisopropylidene-3,4,5,6-tetrahydro-s-triazinium fluorosulfonate (0.600 g, 1.12 mmol) and 50 ml of deionized water were stirred under reflux for a period of 11 hours. During this time, an insoluble white solid gradually appeared on the surface of the then yellow hydrolysate. The colorless solid was collected on a small Büchner funnel and was shown by nmr spectroscopy to be 1,3,5-triphenyl-2,4,6-triisopropylidenehexahydro-s-triazine (0.121 g, 25%).

1,3,5-Triphenyl-2-Isopropyl-4,6-Diisopropylidene-3,4,5,6-Tetrahydro-s-Triazine (104)

1,3,5-Triphenyl-2-isopropyl-4,6-diisopropylidene-3,4,5,6-tetrahydro-s-triazinium fluorosulfonate (1.43 g, 2.60 mmol), and 50 ml of ethanol were combined in a 125 ml erlenmeyer flask equipped with a magnetic stirring bar. Addition of sodium borohydride (0.220 g, 5.28 mmol) in several increments to the stirred triazinium salt mixture resulted in a vigorous reaction with concomitant disappearance of the yellow triazinium salt coloration. After stirring for 15 minutes, 60 ml of water was added. 1,3,5-Triphenyl-2-isopropyl-4,6-diisopropylidene-3,4,5,6-tetrahydro-s-triazine (1.14 g, 99%) was collected on a small Büchner funnel as a white powder. Recrystallization from hot hexanes afforded white prisms which melted broadly at 155-162°; ir (KBr) 1660 and 1670 cm^{-1} (C=C-N); nmr ($COCl_3$) δ 0.73 (doublet,

J=7 Hz, 6H), 1.29 (singlet, 6H), 1.71 (singlet, 6H), 1.70-1.87 (multiplet, 1H), 5.30 (doublet, J=10 Hz, 1H), 6.57-7.50 (multiplet, 15H); m/e (calcd for $C_{31}H_{35}N_3$) 437.2831, (found) 437.2839.

N-(p-Tolyl)-2-Ethylbutyramide (105)

A solution consisting of p-toluidine (23.0 g, 0.215 mole) and triethylamine (13.9 g, 20.0 ml, 0.138 mole) in 250 ml of chloroform was prepared in a 500 ml round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and an ice water cooling bath. 2-Ethylbutyryl chloride (14.4 g, 0.107 mole) in 75 ml of chloroform was added dropwise to the chilled amine solution and the mixture stirred at ambient temperature for 6 hours. The crude product mixture was washed twice with dilute hydrochloric acid, once with 20% sodium carbonate, and finally, with water. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure. The residue was recrystallized from 95% ethanol to yield N-(p-tolyl)-2-ethylbutyramide (17.5 g, 80%) as fine colorless needles: mp 111-112.5° (lit.[93] mp 102.5-108.5°), ir (KBr) 1650 cm^{-1} (C=O), nmr ($CDCl_3$) δ 0.77 1.02 (triplet, J=7 Hz, 6H), 1.13-2.20 (multiplet, 5H), 2.22 (singlet, 3H), 6.95-7.48 (multiplet, 4H), 7.92 (broad, 1H).

Diethylketone-N-(p-Tolyl)imine (106)

N-(p-Tolyl)-2-ethylbutyramide (6.50 g, 31.7 mmol), phosphorus pentachloride (6.60 g, 31.7 mmol), and 50 ml of benzene were combined in a 100 ml round-bottomed flask and the resulting slurry stirred under a reflux for 30 minutes. Evaporation of the benzene and phosphoryl chloride at reduced pressure produced an oily residue which was vacuum

distilled at 101°/0.25 mm Hg. 2-Ethyl-N-(p-tolyl)iminobutyl chloride (6.70 g, 95%) was obtained as a colorless liquid. Ir (liquid film) 1685 cm^{-1} (C=N); nmr ($CDCl_3$) δ 0.95 (triplet, J=7 Hz, 6H), 1.40-2.11 (multiplet, 4H), 2.31 (singlet, 3H), 2.64 (multiplet, J=7 Hz, 1H), 6.67-7.27 (multiplet, 4H)

The above prepared imidoyl chloride (6.71 g, 29.5 mmol), 150 ml of benzene, and triethylamine (30.3 g, 43.5 ml, 0.299 mole) were added consecutively to a 500 ml round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and a nitrogen atmosphere. The mixture was stirred under reflux for 12 hours then filtered through a medium porosity Buchner funnel to remove the precipitated triethylamine hydrochloride. The dark brown filtrate was concentrated at reduced pressure and vacuum distilled at 103-106°/0.65 mm Hg. Diethylketene-N-(p-tolyl)imine (3.50 g, 70%) was obtained as a greenish yellow liquid: Ir (liquid film) 2000 cm^{-1} (C=C=N); nmr ($CDCl_3$) δ 1.08 (triplet, J=7 Hz, 6H), 2.08 (quartet, J=7 Hz, 4H), 2.30 (singlet, 3H), 7.12 (singlet, 4H), m/e (<u>calcd</u> for $C_{13}H_{17}N$) 187.1360, (<u>found</u> 187.1364

<u>Alkylation of Diethylketene-N-(p-Tolyl)imine (106) with Methyl Fluorosulfonate. 1,3,5-Tri-(p-Tolyl)-2,4,6-Tri-(3-Pentylidene)perhydro-s-Triazine (107) and 1,6-Dimethyl-2-(3-Pentyl)-3-(p-Tolyl)-4-(3-Pentylidene)-1,2,3,4-Tetrahydroquinazoline (109)</u>

A solution of diethylketene-N-(p-tolyl)imine (1.50 g, 8.01 mmol) in 50 ml of anhydrous ether was prepared in a 100 ml round-bottomed flask equipped with a magnetic stirring bar under a nitrogen atmosphere. Methyl fluorosulfonate (0.913 g, 0.647 ml, 8.01 mmol) was added, and the mixture stirred at room temperature for 17 hours. The ether was removed at reduced pressure and the pasty yellow residue diluted with 30 ml of absolute ethanol. The colorless crystals of 1,3,5-tri-(p-tolyl)-

2,4,6-tri-(3-pentylidene)perhydro-s-triazine (0.400 g, 26%) which immediately precipitated were collected on a small Buchner funnel and recrystallized from absolute ethanol: mp 209.5-212°; ir ($CDCl_3$) 1640 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 0.725 (triplet, J=7.5 Hz, 18H), 1.92 (quartet, J=7.5 Hz, 12H), 2.23 (singlet, 9H), 6.95 (singlet, 12H), m/e (calcd for $C_{39}H_{51}N_3$) 561.4082, (found) 561.4086. The above mentioned ethanolic filtrate was cooled to 0-5° via an ice water bath, and treated with excess sodium borohydride (0.30 g, 7.9 mmol). The reduction proceeded vigorously with an initial burst of red which gradually faded to pale yellow. The reaction was deemed complete after stirring for 15 minutes at ice temperature. The mixture was quenched with 50 ml of water and the organic soluble components extracted into two 50 ml portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate then evaporated at reduced pressure to an oily residue. Crystallization from 15 ml of ethanol produced 1,6-dimethyl-2-(3-pentyl)-3-(p-tolyl)-4-(3-pentylidene)-1,2,3,4-tetrahydroquinazoline (0.51 g, 34%) as fine white needles: mp 106.5-107.5°, nmr ($CDCl_3$) δ 0.67-1.76 (multiplet, 17H), 2.15 (singlet, 3H), 2.22 (singlet, 3H), 2.27-2.92 (multiplet, 4H), 2.95 (singlet, 3H), 4.76 (doublet, J=8 Hz, 1H, H_2), 6.32 (doublet, $J_{7,8}$=8 Hz, 1H, H_8), 6.58-7.05 (multiplet, 5H), 7.18 (doublet, $J_{5,7}$=2 Hz, 1H, H_5), m/e (could for $C_{27}H_{36}N_2$) 390.3034, (found) 390.3031.

N-Isopropyl 2,2-Diphenylacetamide (1i0)

A solution of isopropylamine (20.0 g, 0.338 mole) triethylamine (27.1 g, 0.268 mole), and 750 ml of chloroform was prepared in a 2000 ml three-necked round-bottomed flask equipped with a mechanical stirrer,

addition funnel, and a calcium sulfate drying tube, then chilled to 0-5° with an ice water bath. 2,2-Diphenylacetyl chloride (62.0 g, 0.268 mole) in 75 ml of chloroform was added dropwise to the amine solution and stirred at ambient temperature for 8 hours. The crude product mixture was washed with dilute hydrochloric acid, water, and, finally, dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded N-Isopropyl-2,2-diphenylacetamide (60.5 g, 89%) as a colorless solid. Recrystallization from hot benzene produced small colorless needles: mp 155-156.5° (lit.[94] mp 158-159°), ir ($CHCl_3$) 1650 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.07 (doublet, J=7 Hz, 6H), 4.17 (heptet, J=7 Hz, 1H), 4.85 (singlet, 1H), 5.48 (broad, 1H), 7.25 (singlet, 10H).

Diphenylketene-N-Isopropylimine (111)

N-Isopropyl-2,2-diphenylacetamide (20.0 g, 79.0 mmol) and 50 ml of benzene were combined in a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. Phosphorus pentachloride (16.4 g, 79.0 mmol) was added to the amide slurry, and the resulting suspension stirred under reflux for 90 minutes. The solvent and phosphoryl chloride were removed by evaporation at reduced pressure. Without further purification, the crude imidoyl chloride was transferred with 250 ml of toluene to a 500 ml round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and a calcium sulfate drying tube. The solution was treated with triethylamine (40.5 g, 0.400 mole, 58.0 ml), then stirred under reflux for 12 hours. Upon cooling, the mixture was passed through a medium porosity Büchner funnel to remove the precipitated triethylamine hydrochloride. The filtrate was concentrated at reduced pressure to a brown liquid

which on vacuum distillation (137-138°/0.1 mm Hg) produced diphenylketene-N-isopropylimine (10.2 g, 55%) as a greenish yellow liquid. The ketenimine solidified on standing and could be recrystallized from petroleum ether (20-40°) to give stout pale yellow needles: mp 45-46.5°, ir ($CHCl_3$) 2000 cm^{-1} (C=C=N), nmr ($CDCl_3$) δ 1.33 (doublet, J=6.5 Hz, 6H), 2.25 (heptet, J=6.5 Hz, 1H), 7.28 (multiplet, 10H), m/e (calcd for $C_{17}H_{17}N$) 235.1360, (found) 235.1361.

Alkylation of Diphenylketene-N-isopropylimine (111) Syn, Anti-N-Isopropyl-2-(N-Methyl-N-isopropyl)amino-3,3-Diphenyl-3-Benzhydrylideneazetidinium Fluorosulfonate (112, 113)

A solution of diphenylketene-N-isopropylimine (3.00 g, 12.7 mmol) and 50 ml of anhydrous ether was prepared in a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. Methyl fluorosulfonate (1.20 ml, 1.69 g, 14.9 mmol) was syringed into this solution and the mixture stirred at room temperature for approximately 12 hours. The ether and unreacted methyl fluorosulfonate were removed from the crude product mixture by evaporation at reduced pressure, and the solid yellow residue recrystallized from ethanol/ether. Colorless prisms of syn, anti-N-isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylideneazetidinium fluorosulfonate (3.00 g, 80.5%) were obtained: mp 25-255° (decomp.), ir ($CHCl_3$) 1710 cm^{-1} (C=N), nmr (trifluoroacetic acid) δ 0.83 (doublet, J=7.0 Hz, 4.5H), 1.42 (doublet, J=7 Hz, 7.2H), 2.82 (singlet,) 65H), 3.39 (sluglet, 2.35H), 3.70-4.78 (multiplet, 2H), 6.57-7.65 (multiplet, 10H).

N-Isopropyl-2-(N-Methyl-N-Isopropyl)amino-3,3-Diphenyl-4-Benzhydrylidene-azetidine (114)

N-Isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylideneazetidinium fluorosulfonate (1.2827 g, 2.195 mmol), and 50 ml of 95% ethanol were combined in a 125 ml erlenmeyer flask and stirred magnetically. Excess sodium borohydride (0.250 g, 6.59 mmol) was added to the heterogeneous mixture in small increments over a period of 5 minutes. During this time, the fluorosulfonate salt was rapidly consumed and was displaced by a fine milky white solid. After stirring at room temperature for an additional 15 minutes, the reaction was quenched with 60 ml of water. The solid was collected by suction filtration on a small Büchner funnel, washed three times with 15 ml portions of water, and, finally, dried under vacuum. N-Isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylideneazetidine (1.0684 g, 99%) was obtained as a colorless powder. Recrystallization from petroleum ether (20-40°) afforded colorless prisms: mp 119-120°, ir ($CHCl_3$) 1640 cm^{-1} (C=C-Ph); nmr ($CDCl_3$) δ 0.95 (doublet, J=7 Hz, 9H), 1.16 (doublet, J=7 Hz, 3H), 1.57 (singlet, 3H), 2.72-3.63 (multiplet, 2H), 5.42 (singlet, 1H), 6.30-7.65 (multiplet, 20H), m/e (calcd for $C_{35}H_{38}N_2$) 486.3034, (found) 486.3022.

Thermolysis of N-Isopropyl-2-(N-Methyl-N-Isopropyl)amino-3,3-Diphenyl-4-Benzhydrylideneazetidine (114)

N-Isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylideneazetidine (0.20 g, 4.11 mmol), was packed into a 5mm o.d. nmr tube and evacuated in a system equipped with an in-line U-tube trap cooled to -78° with a dry-ice/acetone bath. The chamber containing the nmr tube was brushed with a bunsen burner flame until

melting of the azetidine became visible (ca. 120°), then heated intermittently until the sample was reduced to a complete melt. The sample was allowed to cool and resolidify under vacuum, then removed and diluted with deuterochloroform. Spectroscopic analysis of this solution indicated a clean conversion to tetraphenylalleene[68] (0.141 g, 98%, mp 163-164°, lit.[89] mp 164°) with no trace of starting azetidine or formamidine by-products.

Analysis of the contents of the U-tube trap showed only the presence of N-methyl-N-isopropyl-N'-isopropyl formamidine (0.573 g, 98%): mp (micro) 153°; ir (liquid film) 1650 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.08 (doublet, J=7 Hz, 6H), 1.14 (doublet, J=7 Hz, 1H), 3.67 (heptet, J=7 Hz, 1H), 7.33 (singlet, 1H); m/e (calcd for $C_8H_{18}N_2$) 142.1469, (found) 142.1467.

Solvent Dependence Study on the Cycloreversion of N-Isopropyl-2-(N-Methyl,N-Isopropyl)amino-3,3-Diphenyl-4-Benzhydrylidenoazetidine (114)

Approximately 50 mg of N-isopropyl-2-(N-methyl,N-isopropyl)-amino-3,3-diphenyl-4-benzhydrylidenoazetidine were packed into each of five individual nmr tubes, diluted with 0.5 ml of the appropriate solvent, then sealed with nmr tube caps. The samples were immersed together in an oil bath preset at 75° and allowed to remain at this temperature for a period of 5 minutes. The samples were removed from the oil bath and immediately cooled in an ice water bath to check any further cycloreversion. Careful nmr integration of the N-methyl signals of the azetidine and formamidine indicated the extent of cycloreversion:

Solvent	Azetidine	Ferrocidine (ratio)
Pyridine	1.0	1.8
Methylene chloride	1.1	1.0
Chloroform	2.1	1.0
Benzene	3.5	1.0
Toluene	3.6	1.0

Thermolysis of N-isopropyl-2-(N-Methyl-N-Isopropyl)amino-3,3-Diphenyl-4-Benzhydrylidenazetidine (114) in the Presence of Dimethylacetylenedicarboxylate

N-Isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylidenazetidine (0.500 g, 0.103 mmol) was packed into a 5 mm o.d. nmr tube, then diluted with 0.5 ml of deuterochloroform and dimethylacetylenedicarboxylate (0.015 ml, 0.022 g, 0.16 mmol). The tube was capped, immersed in an oil bath pre-set at 75°, and heated at this temperature for 30 minutes. The solution was removed from the tube and evaporated at reduced pressure to remove the volatile components. The brown residue was taken up in deuterochloroform and examined via nmr spectroscopy. Triphenylallene was determined to be present in large amounts, but no N-methyl signal was observed in the region δ 1.5-3.5 as expected for a 4+2 adduct.

Attempted Recrystallization of N-Isopropyl-2-(N-Methyl-N-Isopropyl)-amino-3,3-Diphenyl-4-Benzhydrylidenazetidine (114) from Absolute Ethanol

N-Isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diphenyl-4-benzhydrylidenazetidine (2.50 g, 5.14 mmol) and 25 ml of absolute ethanol were placed in a 50 ml erlenmeyer flask and heated to boiling. After a few minutes, the hot solution was filtered from the undissolved

solids, and the clear colorless filtrate set aside for crystallization. Several hours later, the fine colorless prisms (1.10 g) were collected by suction filtration and dried *in vacuo*. Spectroscopic analysis of this crystalline material and comparison with authentic spectra reported in the literature[68] identified the sample was tetraphenylallene mp 162-163.5° (lit.[89] mp 164°), ir ($CDCl_3$) 1595, 1485 and 1438 cm^{-1} (aromatic stretch and breathing modes); nmr ($CDCl_3$) δ 7.17-7.55 (multiplet).

2-Ethylbutyryl Chloride

2-Ethylbutyric acid (16.5 g, 0.142 mole) and thionyl chloride (24.8 g, 15.0 ml, 0.209 mole) were combined in a 100 ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. After the initial endothermic reaction subsided, the mixture was refluxed for approximately 30 minutes. The condenser was replaced by a fractionating column and the component distilling at 135-138° (lit.[89] bp 138-139°/750 mm Hg) was collected. 2-Ethylbutyryl chloride (18.9 g, 98%) was obtained as a pungent, colorless liquid: ir (liquid film) 1795 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.95 (triplet, J=7 Hz, 6H), 1.07-2.08 (multiplet, 4H), 2.67 (pentet, J=6.5 Hz, 1H).

N-Isopropyl-2-Ethylbutyramide (118)

Isopropylamine (0.46 g, 0.126 mole) and triethylamine (12.8 g, 18.3 ml, 0.126 mole) were combined in a 500 ml round-bottomed flask equipped with an addition funnel and a magnetic stirring bar. 200 Ml of chloroform was added and the mixture cooled to 0-5° with an ice

water bath. 2-Ethylbutyryl chloride (17.0 g, 0.126 mole) in 50 ml of chloroform was added dropwise to the amine mixture, then stirred at ambient temperature for 4 hours. The mixture was transferred to a 500 ml separatory funnel and washed twice with dilute hydrochloric acid, then with water. The organic layer was dried over anhydrous magnesium sulfate and evaporated at reduced pressure to yield N-isopropyl-2-ethylbutyramide (13.4 g, 68%) as a colorless waxy solid. mp 147-149° (lit[95] mp 145-147°); ir ($CHCl_3$) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.70-1.07 (multiplet, 6H), 1.16 (doublet, J=7 Hz, 6H), 1.25-2.00 (multiplet, 5H), 4.20 (heptet, J=7 Hz, 1H), 5.50 (broad, 1H).

Diethylketene-N-Isopropylimine (113)

A solution of triphenylphosphine (8.34 g, 32.0 mmol) in 100 ml of methylene chloride was prepared in a 200 ml round-bottomed flask and chilled to 0-5° with an ice water bath. Bromine (5.08 g, 32.0 mmol) was added dropwise to the stirred triphenylphosphine solution until the first persistence of bromine color. At this point, N-isopropyl-2-ethylbutyramide (5.00 g, 32.0 mmol) and triethylamine (8.05 g, 11.6 ml, 79.0 mmol) were introduced to the mixture. The ice water bath was removed, replaced by a heating mantle, and the reaction flask fitted with a reflux condenser. The suspension was stirred and refluxed gently under a nitrogen atmosphere for a period of 60 minutes. During this time, the mixture became homogeneous and assumed a dark brown appearance. After cooling to room temperature, the methylene chloride was evaporated at reduced pressure and the solid residue triturated twice with 75 ml portions of petroleum ether (20-40°). The pale yellow extracts were combined and concentrated to a yellow liquid.

Vacuum distillation (Kugelrohr) at 30-40°/1 mm Hg produced diethyl ketene-N-isopropylimine (2.10 g, 47%) as a colorless liquid; ir (liquid film) 2010 cm^{-1} (C=C=N), nmr ($CDCl_3$) δ 1.02 (triplet, J=7 Hz, 6H), 1.18 (doublet, J=6.5 Hz, 6H), 1.96 (quartet, J=7 Hz, 4H), 3.53 (heptet, J=6.5 Hz, 1H); m/e (calcd for $C_9H_{17}N$) 139.1360, (found) 139.1357.

Alkylation of Diethylketene-N-Isopropylimine (119) with Methyl Fluorosulfonate: N-Isopropyl-2-(N-Methyl-N-Isopropyl)amino-3,3-Diethyl-4-(3-Pentylidene)azetidine (121)

A solution of diethylketene-N-isopropylimine (3.00 g, 21.6 mmol) in 150 ml of anhydrous ether was prepared in a 250 ml round-bottomed flask equipped with a magnetic stirring bar, and a nitrogen atmosphere. Stirring was begun and the solution cooled to approximately -78° with a dry ice/acetone bath. Freshly distilled methyl fluorosulfonate (2.46 g, 1.74 ml, 21.6 mmol) was syringed into the ketenimine solution and the mixture stirred at this temperature for 4.5 hours. The ether was evaporated at reduced pressure to an orange residue which was immediately taken up in 75 ml of ethanol and reduced at room temperature with excess sodium borohydride (0.819 g, 21.6 mmol). The mixture immediately discharged its orange coloration, and, after 15 minutes of stirring, was quenched with 150 ml of water. Extraction into two 50 ml portions of methylene chloride followed by drying over anhydrous magnesium sulfate and evaporation at reduced pressure afforded crude N-isopropyl-2-(N-methyl-N-isopropyl)amino-3,3-diethyl-4-(3-pentylidene)-azetidine (2.45 g, 78%). Attempted distillation (Kugelrohr) at 95-100°/0.75 mm Hg produced the azetidine (1.29 g) as a colorless liquid in 41% yield but failed to improve its purity. ir (liquid film) 1645 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 0.65-1.58 (multiplet, >24H), 1.66-2.33 (multiplet,

>4H), 2.52 (singlet, 3H), 3.0-3.75 (multiplet, 2H), 5.52 (singlet, 1H); m/e (calcd for $C_{15}H_{38}N_2$) 294.3034, (found) 294.3037.

N,N-Dimethylisobutyramide (124)

Dimethylamine (11.3 g, 0.251 mole), triethylamine (25.2 g, 0.250 mole), and 250 ml of benzene were combined in a 500 ml three-necked round-bottomed flask equipped with a mechanical stirrer, and an ice water cooling bath. Isobutyryl chloride (20.0 g, 0.188 mole) in 50 ml of benzene was added dropwise to the amine solution. The mixture was stirred at ambient temperature for 4 hours, and then filtered from the triethylamine hydrochloride salts. The filtrate was concentrated at reduced pressure to a yellow liquid which on vacuum distillation at 101°/ca 20 mm Hg (lit.[56] bp 178-179°) afforded N,N-dimethylisobutyramide (18.8 g, 86%) as a colorless liquid ir ($CHCl_3$) 1640 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.11 (doublet, J=7 Hz, 6H), 2.84 (multiplet, J=7 Hz, 1H), 3.17 (broad doublet, 6H).

N,N-Dimethyl-1-Chloro-2-Methyl-1-Propenylamine (125)

A solution of N,N-dimethylisobutyramide (30.0 g, 0.261 mole), in 90 ml of anhydrous ether was prepared in a 500 ml three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, and a nitrogen atmosphere. Oxalyl chloride (33.1 g, 0.261 mole) in 75 ml of anhydrous ether was added dropwise to the amide solution. During this time, rapid evolution of gases and the precipitation of a thick white solid occurred. The heterogeneous mixture was diluted with ether and stirred under nitrogen for approximately 12 hours. Triethylamine in 75 ml of anhydrous ether was added dropwise to the

white slurry, and then stirred for an additional 12 hours. The ethereal product mixture was filtered from the precipitated amine salts and concentrated at reduced pressure to a brown liquid. Vacuum distillation at 40°/25 mm Hg (lit.[19] bp 40°/25 mm Hg) produced N,N-dimethyl-1-chloro-2-methyl-1-propenylamine (24.1 g, 69%) as a clear, colorless, hygroscopic liquid: ir ($CHCl_3$) 1635 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 1.77 (singlet, 2.3H) (singlet).

Treatment of N,N-Dimethyl-1-Chloro-2-Methyl-1-Propenylamine (175) with Sodium Bis(trimethylsilyl)amide

A solution of sodium bis(trimethylsilyl)amide (2.75 g, 15.0 mmol) in 30 ml of benzene was prepared in a 250 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a calcium sulfate drying tube. N,N-Dimethyl-1-chloro-2-methyl-1-propenylamine (2.00 g, 14.9 mmol) in 25 ml of benzene was added dropwise over a period of 5 minutes to the stirred silylamide solution. After stirring for 5 hours, the mixture was washed twice with 50 ml portions of water, dried over anhydrous magnesium sulfate, then evaporated to an oily residue (3.15 g). Vacuum sublimation at 50°/0.25 mm Hg produced N,N-dimethyl-1-N,N-bis(trimethylsilyl)amino-2-methyl-1-propenylamine (2.67 g, 70%) as a colorless solid: mp 74-75°; ir ($CHCl_3$) 1645 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 0.08 (singlet, 18H), 1.53 (doublet, 6H), 2.62 (singlet, 6H); m/e (mass) for $C_{12}H_{29}N_2Si_2$ 258.1946, (found) 258.1949.

Treatment of N,N-Dimethyl-1-Chloro-2-Methyl-1-Propenylamine (125) with Potassium t-Butoxide

A suspension of potassium t-butoxide (5.30 g, 46.8 mmol), in 75 ml of dry benzene was prepared in a 250 ml round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and a nitrogen atmosphere. N,N-Dimethyl-1-chloro-2-methyl-1-propenylamine (5.00 g, 37.4 mmol) in 10 ml of benzene was syringed into the t-butoxide suspension. This mixture was then refluxed under nitrogen for 20 hours. The product mixture was washed once with 50 ml of water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a yellow liquid. Vacuum distillation at 30-34°/0.15 mm Hg produced a colorless distillate (2.60 g) which contained some N,N-dimethylisobutyramide (ca. 15%) and a substance whose spectral properties are in agreement with N,N-dimethyl-1-(t-butoxy)-2-methyl-1-propenylamine (ca. 85%), ir (liquid film) 1600 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 1.26 (singlet, 9H), 1.53 (singlet, 3H), 1.60 (singlet, 3H), 2.62 (singlet, 6H).

Treatment of Dimethylketene-N,N-Dimethylimidium Tetrafluoroborate (129) with Sodium Bis(trimethylsilyl)amide

A solution of sodium bis(trimethylsilyl)amide (2.05 g, 11.2 mmol) in 25 ml of anhydrous ether was prepared in a 100 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a nitrogen atmosphere. In a separate vessel, N,N-dimethyl-1-chloro-2-methyl-1-propenylamine (1.50 g, 11.2 mmol) was added to a solution of silver tetrafluoroborate (2.20 g, 11.2 mmol) in 25 ml anhydrous ether. Precipitation of silver chloride occurred immediately. This heterogeneous mixture was rapidly transferred to the addition funnel

via suction filtration through a bed of Celite. The clear dimethylketene-N,N-dimethyliminium tetrafluoroborate solution was added dropwise to the stirred allylamide base solution. After 2 hours of stirring under nitrogen, the mixture was washed once with 50 ml of water, dried over anhydrous magnesium sulfate and evaporated at reduced pressure. Spectroscopic (nmr) analysis of the residue indicated that N,N-dimethylisobutyramide and N,N-dimethyl-1-N,N-bis(trimethylsilyl)amino-2-methyl-1-propenylamine were present in the approximate proportions of 1:2.3.

Treatment of Dimethylketene-N,N-Dimethyliminium Tetrafluoroborate (123) with Potassium t-Butoxide

A suspension of potassium t-butoxide (1.26 g, 11.2 mmol) in 25 ml of dry toluene was prepared in a 100 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and nitrogen atmosphere. In a separate vessel, N,N-dimethyl-1-chloro-2-methyl-1-propenylamine (1.50 g, 11.2 mmol) was added to a solution of silver tetrafluoroborate (2.20 g, 11.2 mmol) in 25 ml of toluene. Immediate precipitation of silver chloride occurred. This heterogeneous mixture was rapidly transferred to the addition funnel *via* suction filtration through a bed of Celite. The clear dimethylketene-N,N-dimethyliminium tetrafluoroborate solution was added dropwise to the stirred t-butoxide base slurry. After approximately 3 hours of stirring under nitrogen, the mixture was filtered, washed twice with 50 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a yellow residue. Spectroscopic (nmr) analysis of this residue indicated that N,N-dimethylisobutyramide and N,N-dimethyl-1-(t-butoxy)-2-methyl-1-propenylamine were the only products.

N,N-Dimethyl-2,2-Diphenylacetamide (130)

A solution consisting of triethylamine (15.6 g, 0.154 mole) dimethylamine (6.92 g, 0.154 mole), and 500 ml of chloroform was prepared in a 1000 ml round-bottomed flask equipped with an addition funnel, mechanical stirrer, and an ice water cooling bath. Diphenylacetyl chloride (35.5 g, 0.154 mole) in 75 ml of chloroform was slowly added to the amine mixture over a period of 15 minutes. The ice bath was removed, and the product mixture was stirred at ambient temperature for 2 hours. After washing with dilute hydrochloric acid and water, the solution was dried over anhydrous magnesium sulfate and then evaporated at reduced pressure to a solid residue. Recrystallization of this material from benzene-petroleum ether (65-110°) afforded N,N-dimethyl-2,2-diphenylacetamide (30.2 g, 82%) as a colorless crystalline solid. mp 130-131° (lit. 97 mp 131-132°). ir ($CHCl_3$) 1645 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.23 (singlet, 3H), 1.27 (singlet, 3H), 5.20 (singlet, 1H), 7.24 (singlet, 10H).

N,N-Dimethyl-1-Chloro-2,2-Diphenylethenylamine (131)

A solution of N,N-dimethyl-2,2-diphenylacetamide (10.0 g, 41.8 mmol) in 50 ml of chloroform was prepared in a 200 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. Phosphorus pentachloride (8.69 g, 41.8 mmol) was added and the resulting mixture stirred under reflux for 5 hours. The solvent and phosphoryl chloride were removed at reduced pressure and the remaining traces of phosphoryl chloride chased with 50 ml of chloroform. The residue was treated with a solution of triethylamine (6.36 g, 10.0 ml, 68.8 mmol) in 80 ml of chloroform. After stirring

for 12 hours, under a blanket of nitrogen, the solvent was removed by evaporation at reduced pressure and the residue triturated three times with 50 ml portions of petroleum ether (20-40°). The combined extracts were evaporated at reduced pressure then pumped at high vacuum to give N,N-dimethyl-1-chloro-2,2-diphenylethenylamine (5.07 g, 47%) as a hygroscopic, yellow oil. Ir ($CHCl_3$) 1680, 1652 cm^{-1} (doublet, C=C-N); nmr ($CDCl_3$) δ 3.35 (singlet, 6H), 7.33 (singlet, 10H).

Treatment of N,N-Dimethyl-1-Chloro-2,2-Diphenylethenylamine (131) with Sodium Bis(trimethylsilyl)amide

A slurry of sodium bis(trimethylsilyl)amide (1.35 g, 7.37 mmol) in 25 ml of benzene was prepared in a 250 ml round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and a nitrogen atmosphere. N,N-Dimethyl-1-chloro-2,2-diphenylethenylamine (1.90 g, 7.37 mmol) in 50 ml of benzene was transferred to the addition funnel and added slowly to the stirred silylamide. The solution immediately developed a brownish color and continued to darken as the addition progressed. After 1 hour, the deep red benzene solution was washed twice with 50 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a dark residue. This mass was triturated three times with 40 ml portions of petroleum ether (30-60°). The combined extracts were filtered and evaporated to a dark brown oil (1.1 g). Infrared spectral analysis of this oil showed an intense band at 2000 cm^{-1} characteristic of a ketenimine functionality. The product was assigned the diphenylketene-N-methylimine structure and was not investigated further.

N-Methylisobutyramide

A mixture consisting of 40% aqueous methylamine (114 ml, 1.50 mole), sodium carbonate (78.4 g, 0.740 mole) and 400 ml of benzene was prepared in a 1000 ml three-necked round-bottomed flask equipped with an addition funnel, mechanical stirrer, and an ice water cooling bath. Isobutyryl chloride (114 g, 1.11 mole) in 100 ml of benzene was added dropwise to the amine solution. This mixture was stirred at ice temperature for 2 hours. The benzene layer was removed, dried over anhydrous magnesium sulfate, and then evaporated at reduced pressure. Vacuum distillation of the residue at 110-112°/17 mm Hg (lit.[98] bp 110°/17 mm Hg) gave N-methylisobutyramide (76.5 g, 68.2%) as a colorless liquid. ir (liquid film) 3200 (N-H), 1650 (C=O), 1550 cm^{-1} (N-H, bend); nmr ($CDCl_3$) δ 1.14 (doublet, J=7 Hz, 6H), 2.50 (heptet, J=7 Hz, 1H), 2.52 (singlet, 3H), 2.66 (singlet, 3H)

N-Methyl-N-Benzylisobutyramide (132)

N-Methylisobutyramide (10.1 g, 0.100 mole), 57% sodium hydride dispersion (4.17 g, 0.100 mole) and 200 ml of dry xylene were combined in a 500 ml three-necked round-bottomed flask equipped with an addition funnel, reflux condenser, magnetic stirring bar, and a nitrogen atmosphere. The mixture was stirred and refluxed under nitrogen for 12 hours before cooling to just above room temperature. A mixture of benzyl chloride (25.3 g, 0.200 mole) in 50 ml of dry xylene was added slowly to the above prepared sodium N-methylisobutyramide, and stirred again under reflux for 8 hours. The hot product mixture was filtered through a bed of Celite to remove the precipitated salts and the filtrate evaporated at reduced pressure to a dark brown liquid.

Vacuum distillation at 115-5°/0.50 mm Hg produced N-methyl-N-benzylisobutyramide (17.6 g, 93%) as a colorless liquid. ir (liquid film) 1645 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.10 (doublet, J=7 Hz, 6H), 2.85 (multiplet, J=7 Hz, 1H), 2.93 (singlet, 3H), 4.58 (singlet, 2H), 7.1-7.4 (multiplet, 5H); m/e (calcd for $C_{12}H_{17}NO$) 191.1309, (found) 191.1309.

N-Methyl-N-Benzyl-1-Chloro-2-Methyl-1-Propenylamine (133)

A solution of N-methyl-N-benzylisobutyramide (10.- g, 52.3 mmol) in 75 ml of anhydrous ether was prepared in a flame dried 500 ml three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, and a nitrogen atmosphere. Oxalyl chloride (6.64 g, 52.3 mmol) in 80 ml of anhydrous ether was added dropwise to the amide solution then stirred for 24 hours. During this time, slow evolution of gases took place with the separation of an oily liquid from the ethereal. Triethylamine (5.29 g, 52.3 mmol) in 25 ml of ether was added slowly to the above mixture and the suspension stirred for 8 hours before being filtered through a bed of Celite. The filter cake was washed with ether and the combined filtrates evaporated at reduced pressure to an amber liquid. Vacuum distillation at 72°/0.5 mm Hg produced N-methyl-N-benzyl-1-chloro-2-methyl-1-propenylamine (7.50 g, 68%) as a yellow liquid. ir ($CHCl_3$) 1635 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 1.67 (singlet, 6H), 2.38 (singlet, 3H), 3.70 (singlet, 2H), 7.1-7.4 (multiplet, 5H); m/e (calcd for $C_{12}H_{16}NCl$) 207.0971, (found) 209.0969

Treatment of N-Methyl-N-Benzyl-1-Chloro-2-Methyl-1-Propenylamine (133) with Sodium Bis(trimethylsilyl)amide

A slurry of sodium bis(trimethylsilyl)amide (1.75 g, 9.55 mmol) in 25 ml of benzene was prepared in a 200 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar and a nitrogen atmosphere. A solution of N-methyl-N-benzyl-1-chloro-2-methyl-1-propenylamine (2.00 g, 9.55 mmol) in 25 ml of benzene was transferred to the addition funnel and added dropwise to the stirred silylamide. After stirring for 8 hours, the mixture was washed twice with 100 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a yellow residue. Vacuum distillation at 124-125°/0.075 mm Hg afforded N-methyl-N-benzyl-1-N,N-bis(trimethylsilyl) amino-2-methyl-1-propenylamine (2.10 g, 66%) slightly contaminated with N-methyl-N-benzylisobutyramide. Ir (CCl_4) 1640 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 0.15 (singlet, 18H), 1.63 (singlet, 6H), 2.57 (singlet, 3H), 4.04 (singlet, 2H), 7.3 (singlet, 5H), m/e (calcd for $C_{18}H_{34}N_2Si_2$) 334.2260, (found) 334.2248.

Treatment of N-Methyl-N-Benzyl-1-Chloro-2-Methyl-1-Propenylamine (133) with Potassium t-Butoxide

A slurry of potassium t-butoxide (3.00 g, 26.7 mmol) in 25 ml of benzene was prepared in a 200 ml round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and a nitrogen atmosphere. N-Methyl-N-benzyl-1-chloro-2-methyl-1-propenylamine (4.00 g, 19.1 mmol) in 25 ml of benzene was added in one portion to the potassium t-butoxide slurry and the resulting suspension stirred under reflux for 8 hours. The reaction was quenched with water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a golden residue (4.38 g).

Vacuum distillation at 95-96.5°/0.5 mm Hg produced a mixture of [illegible] N-benzyl-1-(t-butoxy)-2-methyl-1-propenylamine. A molar ratio of 3.2:1 for the t-butoxy adduct and amide respectively was obtained by integration of the N-methyl nmr spectral signal for each compound: ir (liquid film) 1660 cm^{-1} (C=C-N), nmr ($CDCl_3$) δ 1.32 (singlet, 9H), 13.8 (singlet, 3H), 1.66 (singlet, 3H), 2.57 (singlet, 3H), 3.94 (singlet, 2H), 7.25 (singlet, 5H).

Ethyl N-Methylglycinate (137)

Methylamine (52.0 g, 1.68 mole) and 900 ml of anhydrous ether were combined in a 2000 ml three-necked round-bottomed flask equipped with a mechanical stirrer, 500 ml addition funnel, and an ice water cooling bath. Ethyl bromoacetate (140 g, 0.838 mole) in 350 ml of ether was added slowly to the stirred amine solution over a period of 15-20 minutes. Stirring was continued as the ice water bath gradually warmed to room temperature. After 2 hours, the ethereal mixture was filtered from the precipitated salts and concentrated at reduced pressure. Vacuum distillation of the residue at 60°/27 mm Hg (lit.[99] bp 43°/10 mm Hg) produced ethyl N-methylglycinate (57.0 g, 58%) as a colorless liquid: ir ($CHCl_3$) 3250 (N-H), 1735 cm^{-1} (C=O), nmr ($CDCl_3$) δ 1.28 (triplet, J=7 Hz, 3H), 1.58 (broad singlet, 1H), 2.45 (singlet, 3H), 3.35 (singlet, 2H), 4.20 (quartet, J=7 Hz, 2H).

N-Methyl-N-Carbethoxymethylisobutyramide (138)

A solution consisting of ethyl N-methylglycinate (67.5 g, 0.577 mole), triethylamine (58.4 g, 0.577 mole) and 600 ml of chloroform was prepared in a 1000 ml round-bottomed flask equipped with an addition

funnel and a magnetic stirring bar. Isobutyryl chloride (61.4 g, 0.577 mole) in 100 ml of chloroform was added slowly to the chilled amide solution, then stirred at ambient temperature for 8 hours. The product mixture was concentrated at reduced pressure, diluted with ether, and filtered from the precipitated hydrochloride salts. The filtrate was concentrated at reduced pressure to a yellow liquid. Vacuum distillation at 89°/0.3 mm Hg produced N-methyl-N-carbethoxymethylisobutyramide (91.0 g, 84%) as a pale yellow liquid. Ir ($CHCl_3$) 1735 (C=O, ester), 1640 cm^{-1} (C=O, amide), nmr ($CDCl_3$) δ 1.15 (doublet, J=7 Hz, 6H), 1.28 (triplet, J=7 Hz, 3H), 2.92 (multiplet, J=7 Hz, 1H), 3.15 (singlet, 3H), 4.12 (singlet, 2H), 4.21 (quartet, J=7 Hz, 2H); m/e (<u>calcd</u> for $C_9H_{17}NO_3$) 187.1207, (<u>found</u>) 187.1207.

<u>N-Methyl-N-Carbethoxymethyl-1-Chloro-2-Methyl-1-Propenylamine (135)</u>

A solution of N-methyl-N-carbethoxymethylisobutyramide (9.10 g, 48.6 mmol) in 20 ml of anhydrous ether was prepared in a 300 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a calcium sulfate drying tube. Oxalyl chloride (6.16 g, 48.6 mmol) in 20 ml of ether was added dropwise to the amide solution then stirred at room temperature for 24 hours. The mixture was cooled to 0-5° with an ice water bath, and treated with triethylamine (4.92 g, 48.6 mmol) in 100 ml of ether. The slurry was stirred at ambient temperature for 12 hours, then filtered through a bed of Celite. The brown filtrate was concentrated at reduced pressure to a dark brown liquid which was vacuum distilled at 75-77°/0.55 mm Hg. N-Methyl-N-carbethoxymethyl-1-chloro-2-methyl-1-propenylamine (2.51 g, 23%) was obtained as a hygroscopic, colorless liquid: Ir (CH_2Cl_2) 1735 cm^{-1}

(C=O), 1640 (C=C-N); nmr (CCl_4) δ 1.[illegible]1 (triplet, J=7 Hz, 3H), 1.72 (singlet, 3H), 1.85 (singlet, 3H), 2.47 (singlet, 3H), 3.27 (singlet, 2H), 4.08 (quartet, J=7 Hz, 2H), m/e (calcd for $C_9H_{16}NO_2Cl$) 205.0869, (found) 205.0875.

A sample of the above α-chloroenamine was allowed to stand for 5 days in an nmr tube in solution with deuterochloroform. Analysis of this solution via nmr spectroscopy showed the complete disappearance of signals associated with the α-chloroenamine. In addition to signals corresponding to N-methyl-N-carbethoxymethylisobutyramide, resulting from some hydrolysis, there appeared lines at δ 1.47 (doublet, J=7 Hz), 1.52 (triplet, J=7 Hz), 3.88 (multiplet, J=7 Hz), 4.27 (singlet), 4.44 (quartet, J=7 Hz), and 8.25 (singlet). The structure has been assigned as N-methyl-2-isopropyl-5-ethoxyoxazolinium chloride. Sodium borohydride reduction of an ethanolic solution of the above mixture produced, in addition to N-methyl-N-carbethoxymethylisobutyramide, a substance whose spectral properties are identical to those of ethyl N-methyl-N-isobutylglycinate.

Treatment of N-Methyl-N-Carbethoxymethyl-1-Chloro-2-Methyl-1-Propenylamine (139) with Potassium t-Butoxide

A slurry of potassium t-butoxide (0.749 g, 6.67 mmol) in 10 ml of anhydrous ether was prepared in a 100 ml round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a nitrogen atmosphere. A solution of N-methyl-N-carbethoxymethyl-1-chloro-2-methyl-1-propenylamine (0.315 g, 4.45 mmol) in 20 ml of anhydrous ether was added dropwise to the stirred t-butoxide suspension. Small yellow bursts appeared on each drop made contact with the base, but this coloration quickly faded. After 12 hours of stirring, the

mixture was passed through a bed of anhydrous magnesium sulfate, and the golden ether solution evaporated at reduced pressure to a greenish oil (0.61 g). Vacuum distillation at 85 100°/0.25 mm Hg produced a pale yellow liquid (0.53 g). Nmr spectral analysis of this material indicated a mixture composed mostly of N-methyl-N-carbethoxymethylisobutyramide with much lower intensity (<5%) resonances appearing at δ 1.63 (doublet), 2.43 (singlet), and 5.63 (singlet) in the relative ratios of 6:3:1 respectively. These signals are thought to be associated with N-methyl-2-isopropylidene-5-ethoxomazoline.

N-Carbethoxymethylisobutyramide (142)

A mixture consisting of ethyl glycinate hydrochloride (26.2 g, 0.188 mole) isobutyryl chloride (20.0 g, 0.188 mole), and 100 ml of benzene was prepared in a 300 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The slurry was stirred under reflux for 20 hours, and then filtered from the remaining solids. The filtrate was concentrated at reduced pressure to a residue and vacuum distilled at 100-104°/0.75 mm Hg (lit.[74] mp 82-85°/0.05 mm Hg). N-Carbethoxymethylisobutyramide (20.5 g, 91%) was collected as a colorless liquid: ir ($CHCl_3$) 1735 (C=O, ester, 1660 cm^{-1} (C=O, amide); nmr ($CDCl_3$) δ 1.17 (doublet, J=7 Hz, 6H), 1.27 (triplet, J=7 Hz, 3H), 2.45 (multiplet, J=7 Hz, 1H), 3.98 (doublet, J_{NH,CH_2}=5 Hz, 2H), 4.18 (quartet, J=7 Hz, 2H), 6.12 (broad, 1H).

2-Isopropyl-5-Ethoxyoxazole (143)

A solution of N-carbethoxymethylisobutyramide (25.0 g, 0.144 mole) in 50 ml of chloroform was prepared in a 250 ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. Phosphorus

pentachloride (33.0 g, 0.159 mole) was added to the amide solution. The mixture was stirred under reflux for 90 minutes then overnight at room temperature. The orange solution was evaporated at reduced pressure to remove solvent and phosphoryl chloride, then treated with a solution of triethylamine (27.8 g, 0.275 mole) in 100 ml of benzene. This mixture was refluxed for 2 hours. The solution was filtered free of the precipitated hydrochloride salts and evaporated at reduced pressure to a brown liquid. Vacuum distillation at 53-55°/2 mm Hg (lit.[74] bp 71.5-72°/12 mm Hg) afforded 2-isopropyl-5-ethoxyoxazole (18.9 g, 85%) as a colorless liquid. Ir ($CHCl_3$) 1620 cm^{-1} (O-C=N), nmr ($CDCl_3$) δ 1.27 (doublet, J=7 Hz, 6H), 1.38 (triplet, J=7 Hz, 3H), 2.92 (heptet, J=7 Hz, 1H), 4.02 (quartet, J=7 Hz, 2H), 5.87 (singlet, 1H).

N-Methyl-2-isopropyl-5-Ethoxyoxazolium Fluorosulfonate (144)

A solution of 2-isopropyl-5-ethoxyoxazole (1.30 g, 8.37 mmol) in 25 ml of anhydrous ether was prepared in a 50 ml round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. Methyl fluorosulfonate (1.41 g, 1.00 ml, 12.4 mmol) was syringed in the above ethereate. The mixture clouded almost immediately, and, after approximately five minutes, the product began to separate from the solution as a colorless oil. Stirring was continued for 2 hours, then placed on a rotary evaporator where most of the solvent and excess methyl fluorosulfonate were removed. The residual traces of solvent were removed by pumping under high vacuum for at least 8 hours. N Methyl-2-isopropyl-5-ethoxyoxazolium fluorosulfonate (2.08 g, 92%) was obtained as a pale yellow oil. Ir ($CHCl_3$) 1670 cm^{-1} (O-C=N), nmr ($CDCl_3$) δ 1.41 (doublet, J=7 Hz, 6H), 1.47 (triplet, J=7 Hz, 3H), 3.52 (heptet, J=7 Hz, 1H), 3.88 (singlet, 3H),

4.30 (quartet, J=7 Hz, 2H), 6.93 (singlet, 1H).

Reduction of N-Methyl 2-Isopropyl-5 Ethoxyoxazolinium Fluorosulfonate (144) with Sodium Borohydride. Ethyl-N-Methyl-N-Isobutylglycinate (145)

A solution of N-methyl-2-isopropyl-5-ethoxyoxazolinium fluorosulfonate (1.00 g, 3.72 mmol) in 25 ml of ethanol was prepared in a 125 ml Erlenmeyer flask and chilled to 0-5° with an ice water bath. Excess sodium borohydride (0.141 g, 3.72 mmol) was added in several small increments and then stirred at ambient temperature for 30 minutes. The mixture was concentrated to a residue at reduced pressure. This residue was taken up in 25 ml of methylene chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure produced ethyl-N-methyl-N-isobutylglycinate (0.630 g, 99%) as a colorless liquid. An analytical sample was prepared by vacuum distillation (Kugelrohr) at 90-100°/3 mm Hg. ir ($CHCl_3$) 1735 cm^{-1} (C=O), nmr ($CDCl_3$) δ 0.88 (doublet, J=6 Hz, 6H), 1.25 (triplet, J=7 Hz, 3H), 1.73 (multiplet, 1H), 2.24 (doublet, J=7 Hz, 2H); m/e (calcd for $C_9H_{19}NO_2$) 173.1415, (found) 173.1408.

t-Butylisonitrile (9)

t-Butylisonitrile was prepared from N-t-butylformamide according to the method described by Ugi and Coworkers[100] bp 92-93°/750 mm Hg, ir (liquid film) 2125 cm^{-1} (-N≡C), nmr (CCl_4) δ 1.43 (triplet, J=2 Hz).

Ethyl trans 1,3-Diphenyl-2-Aziridinecarboxylate (153)

Ethyl trans-1,3-diphenyl-2-aziridinecarboxylate was prepared by the Darzens condensation of benzaldehyde with ethyl chloroacetate according to the method described by Deyrup[79] mp 82-83.5° (lit[79]

mp 82-84°), ir (Nujol) 1730 cm^{-1}, nmr (CCl_4) δ 1.08 (triplet, J=7 Hz, 3H), 3.08 (doublet, J=2 Hz, 1H, H_2), 3.72 (doublet, J=2 Hz, 1H, H_3), 4.07 (quartet, J=7 Hz, 2H), 6.7-7.4 (multiplet, 10H).

Thermolytic Isomerization of Ethyl trans-1,3-diphenyl-2-aziridinecarboxylate (153) in Carbon Tetrachloride

Ethyl trans-1,3-diphenyl-2-aziridinecarboxylate (0.2400 g, 0.9737 mmol) and approximately 1 ml of carbon tetrachloride were placed in a 5 mm o.d. nmr tube, and sealed with a nmr tube cap. The mixture was heated for 24 hours at 80° by suspending the tube inside a flask of refluxing benzene so that the reflux completely encompassed the carbon tetrachloride-aziridine solution. The cis/trans isomer distribution was assayed spectroscopically by careful integration of the observed aziridine ring proton signals, and was shown to be approximately 64(±0.7)% cis and 36(±0.7)% trans.

nmr	trans	H_3	δ 3.72 (2.0 Hz)
		H_2	3.08 (2.0 Hz)
	cis	H_3	3.44 (7.0 Hz)
		H_2	3.04 (7.0 Hz)

Thermolysis of Ethyl trans-1,3-Diphenyl-2-Aziridinecarboxylate (153) in t-Butylisocyanide (9)

Ethyl trans-1,3-diphenyl-2-aziridinecarboxylate (0.2800 g, 1.048 mmol) and t-butylisonitrile (0.7700 g, 0.278 mmol) were placed in a 5 mm o.d. nmr tube, capped, then warmed in a steam bath until the aziridine had completely dissolved. The mixture was heated for 24 hours at 80° by suspending the tube inside a flask of refluxing benzene so that the reflux encompassed the isonitrile-aziridine solution. The

tube's contents were analyzed spectroscopically by examining the nmr spectrum in the region δ 2.50-6.00. No signals expected of a 3+1 adduct were observed. Instead, isomerization of the aziridine took place to the extent of approximately 38(±0.6)% cis and 62(±0.6)% trans as determined by careful integration of the signals associated with the aziridine ring protons.

Addition of t-Butylisonitrile (9) to Ethyl trans-1,3-diphenyl-2-Aziridinecarboxylate (153). Phenyl-(N-Phenyl-N-Carbethoxymethyl)-aminoketone-N'-t-Butylimine (155).

Ethyl trans-1,3-diphenyl-2-aziridinecarboxylate (3.204 g, 12.00 mmol), t-butylisonitrile (1.992 g, 24.00 mmol) and 24 ml of carbon tetrachloride were sealed in a pyrex tube. The mixture was positioned in a tube furnace preset at 80° and allowed to remain undisturbed at this temperature for a period of 80 hours. The tube was opened and its contents transferred to a round-bottomed flask. The volatile components were removed by evaporation at reduced pressure. The oily yellow residue was chromatographed on 10% deactivated alumina with cyclohexane as an eluant. Phenyl-(N-phenyl-N-carbethoxymethyl)aminoketone-N'-t-butylimine (7.70 g, 92%) was collected as a yellow band and evaporated in vacuo to a golden oil: ir (CCl_4) 2000 (C=C=N), 1745 cm^{-1} (C=O, ester); nmr (CCl_4) δ 1.23 (quartet, J=7 Hz, 2H), 4.16 (singlet, 2H), δ 43-7.37 (multiplet, 10H), mass spectrum m/e 350 (P^+).

Acid Catalyzed Hydrolysis of Phenyl-(N-Phenyl-N-Carbethoxymethyl) aminoketone-N'-t-Butylimine (155). 2-Phenyl-2-(N-Phenyl-N-Carbethoxymethyl)amino-N'-t-Butylacetamide (159)

A solution consisting of phenyl-(N-phenyl-N-carbethoxymethyl)-aminoketone-N'-t-butylimine (1.80 g, 5.14 mmol) in 50 ml of acetone

was prepared in a 125 ml erlenmeyer flask containing a magnetic stirring bar. Five drops of water were added to this solution followed by three drops of concentrated hydrochloric acid. At this point, the mixture immediately developed a reddish brown color. The solution was heated almost to reflux and water added dropwise until the turbidity persisted. Neutralization with 20% sodium carbonate produced a brilliant yellow solution. The organic soluble components were extracted with carbon tetrachloride, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a yellow orange oil. The oil was applied to a silica gel column and eluted first with chloroform carbon tetrachloride (25:75), and then with chloroform. The second fraction (chloroform) contained 2-phenyl-2-(N-phenyl-N-carbethoxymethyl)amino-N'-t-butylacetamide (0.87 g, 45%) as a pale yellow oil. Purity was established by the observance of a single spot in TLC. ir (CCl_4) 3275 (NH, stretch), 1735 (C=O, ester), 1670 (C=O, amide), 1540 cm^{-1} (NH, bend), nmr (CCl_4) δ 1.23 (triplet, J=7 Hz, 3H), 1.27 (singlet, 1H), 3.68 (singlet, 2H), 4.13 (quartet, J=7 Hz, 2H), 5.08 (singlet, 1H), 6.45-7.40 (multiplet, 10H), 8.08 (broad, 1H).

Phenylacetyl Chloride

Phenylacetic acid (13.6 g, 0.10 mole) and thionyl chloride (35.7 g, 21.6 ml, 0.30 mole) were combined in a 250 ml round-bottomed flask and refluxed for 60 minutes. The excess thionyl chloride was evaporated at reduced pressure. Vacuum distillation of the residue at 55-60°/0.55 mm Hg (lit[89] bp 110-111°/23 mm Hg) afforded phenylacetyl chloride (14.5 g, 94%) as a pungent, colorless liquid: ir (liquid film)

1800 cm^{-1} (C=O), nmr (neat) δ 3.80 (singlet, 2H), δ 8.3-7.30 (multiplet, 5H).

2-Bromo-2-Phenylacetyl Bromide (162)

Phenylacetyl chloride (14.5 g, 93.8 mmol) and bromine (15.0 g, 93.8 mmol) were combined in a 100 ml round-bottomed flask equipped with a reflux condenser and a small magnetic stirring bar. The flask was immersed in a silicone oil bath pre-set at 120°, and the mixture stirred at this temperature for approximately 90 minutes. The product mixture was vacuum distilled at 80°/cm. 0.04 mm Hg (lit.[101] bp 156-158°/24 mm Hg) to give 2-bromo-2-phenylacetyl bromide (21.6 g, 83%) as a colorless liquid. ir (liquid film) 1786 cm^{-1} (C=O), nmr (CCl_4) δ 5.57 (singlet, 0.24H), 5.63 (singlet, 0.76H), 7.15-7.5 (multiplet, 5H).

2-Bromo-2-Phenyl-N-t-Butylacetamide (160)

A solution consisting of t-butylamine (5.85 g, 8.40 ml, 79.9 mmol), triethylamine (8.05 g, 11.2 ml, 79.5 mmol) and 250 ml of benzene was prepared in a 500 ml three-necked round-bottomed flask equipped with an addition funnel and a mechanical stirrer. This mixture was stirred and cooled to 0-5° with an ice water bath while a solution of 2-bromo-2-phenylacetyl bromide (21.0 g, 75.6 mmol) in 75 ml of benzene was added dropwise over a period of 20 minutes. After stirring for an additional 30 minutes, the triethylamine hydrobromide was removed by suction filtration. The filtrate was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, concentrated at reduced pressure, and set aside for crystallization. 2-Bromo-2-phenyl-N-t-butylacetamide (10.7 g, 52%) was obtained as small colorless prisms

Recrystallization from benzene provided an analytical sample: mp [illegible] 134.3°; ir (KBr) 3213 (NH, stretch), 1656 cm^{-1} (C=O); nmr ($CDCl_3$) [illegible] (singlet, 9H), 5.32 (singlet, 1H), 6.43 (broad, 1H), 7.18-7.50 (multiplet, 5H).

Anal. Calcd for $C_{12}H_{16}NOBr$: C, 53.35; H, 3.97; N, 3.18; Br, 29.57. Found: C, 53.43; H, 3.99; N, 3.10; Br, 29.42.

Ethyl N-Phenylglycinate (161)

Ethyl bromoacetate (24.9 g, 0.149 mole), aniline (27.8 g, 0.299 mole) and 100 ml of benzene were combined in a 250 ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. The mixture was stirred under reflux for 12 hours, cooled to room temperature, then filtered from the precipitated anilinium hydrobromide (23.3 g, 0.133 mole, 90.6%). The filtrate was evaporated to dryness, and the residue dissolved in a minimum amount of 95% ethanol. Ethyl N-phenylglycinate (16.7 g, 63%) was produced as a pale yellow crystalline solid: mp 35-56.7° (lit.[102] mp 32°); ir ($CHCl_3$) 3350 (NH, stretch), 1733 cm^{-1} (C=O), nmr (CCl_4) δ 1.23 (triplet, J=7 Hz, 3H), 3.73 (singlet, 2H), 4.13 (quartet, J=7 Hz, 3H), 6.28-7.22 (multiplet, 5H).

Independent Synthesis of 2-Phenyl-2-(N-Phenyl-N-Carbethoxymethyl)-amino-N-t-Butylacetamide

Ethyl N-phenylglycinate (3.10 g, 17.3 mmol), 2-bromo-2-phenyl-N-t-butylacetamide (4.30 g, 16.7 mmol), triethylamine (1.72 g, 2.47 ml, 17.0 mmol), and 15 ml of benzene were combined in a 30 ml round-bottomed flask and refluxed for four days. The precipitated triethylamine hydrobromide was removed by suction filtration. The filtrate was washed with dilute hydrochloric acid, 20% sodium carbonate, and, finally, dried over

anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 2-phenyl-2-(N-phenyl-N-carbethoxymethyl)amino-N'-t-butylacetamide (6.00 g, 98%) as a pale yellow oil. An analytically pure sample was prepared by chromatographing approximately 2.0 g of the above amide on a silica gel column packed in chloroform carbon tetrachloride (25:75). Nine 10 ml fractions were collected by eluting with chloroform carbon tetrachloride (25:75), the last three of which were shown by TLC analysis to contain products completely free of trace impurities. These were combined, evaporated at reduced pressure, and then overnight at high vacuum. The resulting yellow oil exhibited the following properties: ir (CCl_4) 3275 (NH, stretch) 1735 (C=O, ester), 1670 (C=O, amide), 1540 cm^{-1} (NH, bend), nmr (CCl_4) δ 1.16 (triplet, J=7 Hz, 3H), 1.28 (singlet, 9H), 3.68 (singlet, 2H), 4.05 (quartet, J=7 Hz, 2H), 5.10 (singlet, 1H), 6.33-7.32 (multiplet, 10H), 8.15 (broad, 1H).

<u>Anal.</u> Calcd for $C_{22}H_{28}N_2O_3$: C, 71.69; H, 7.67; N, 7.60.
Found: C, 71.47; H, 7.77; N, 7.52.

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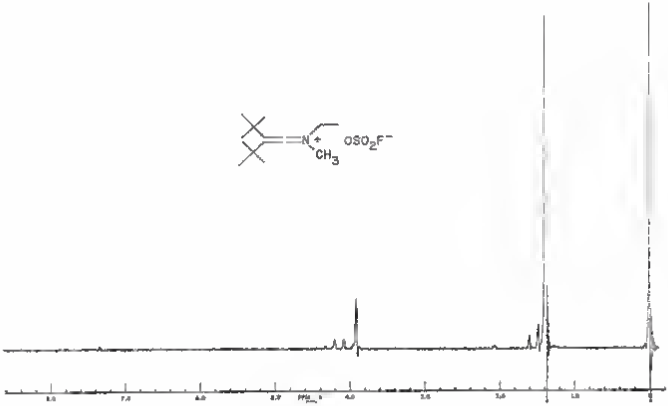
NMR SPECTRA



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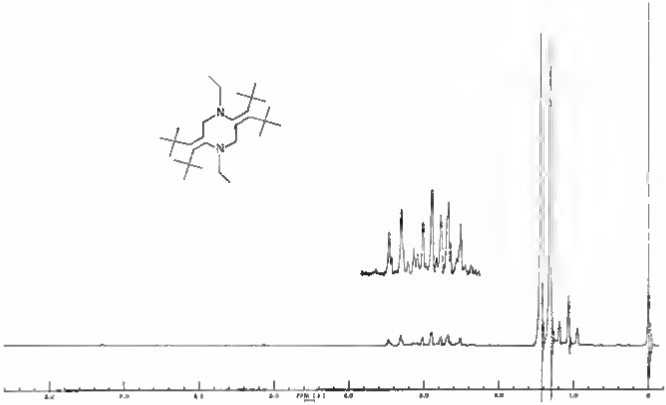

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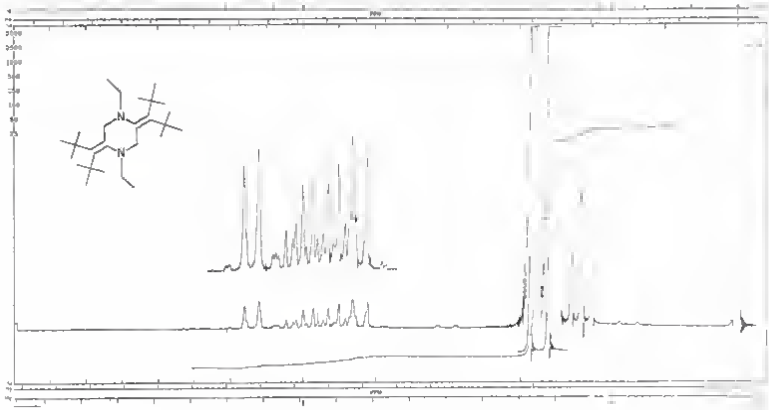

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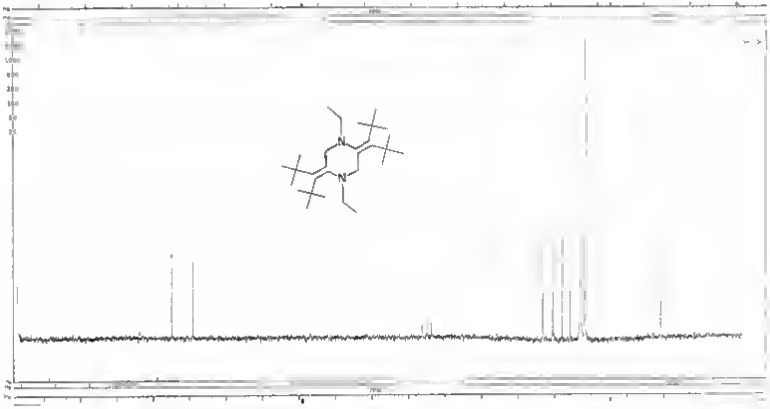

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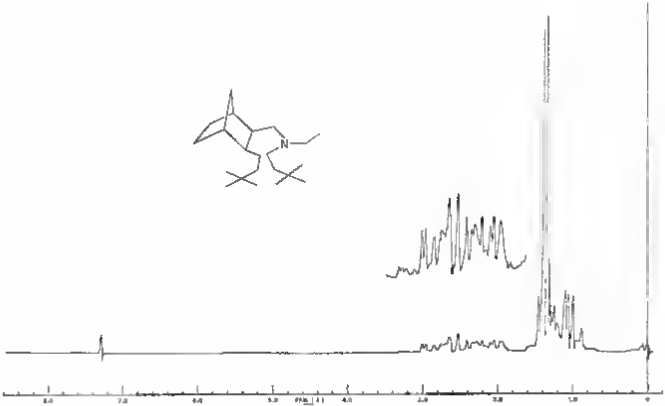

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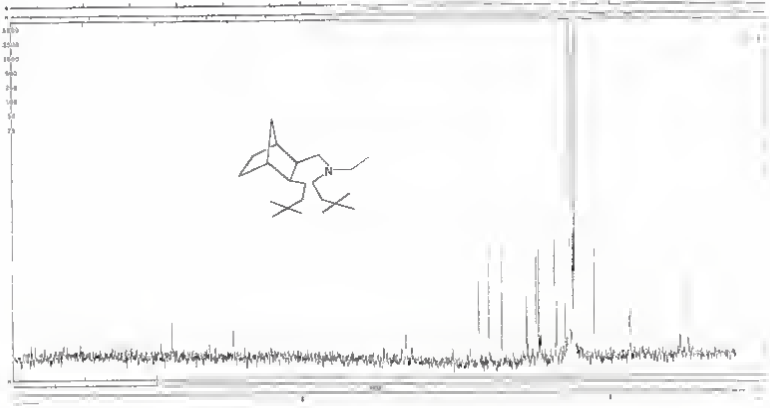

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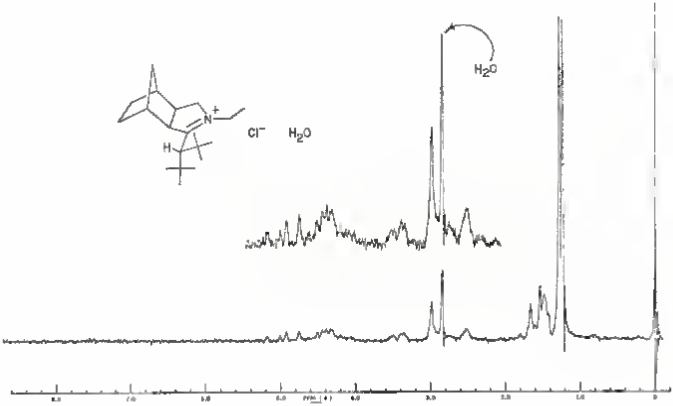

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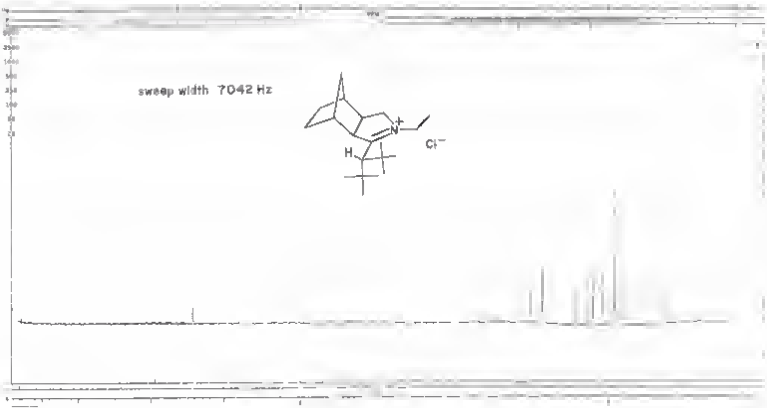

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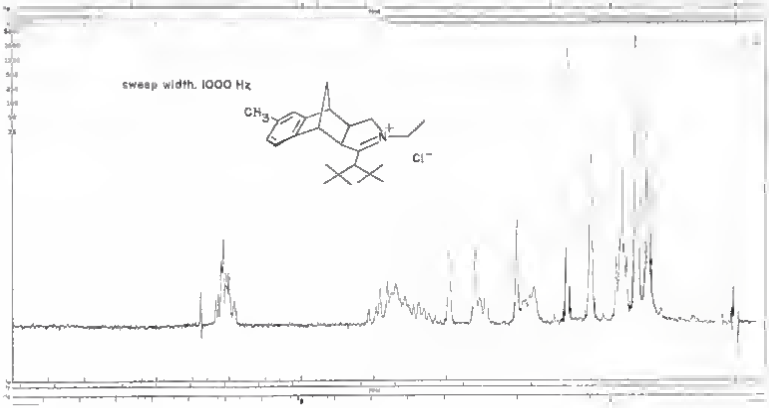

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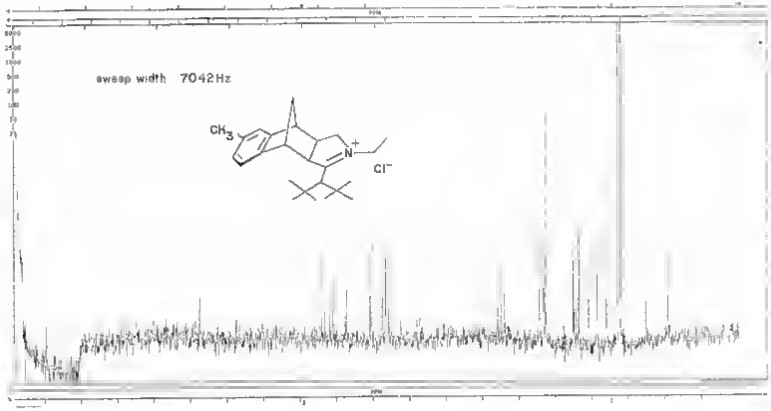

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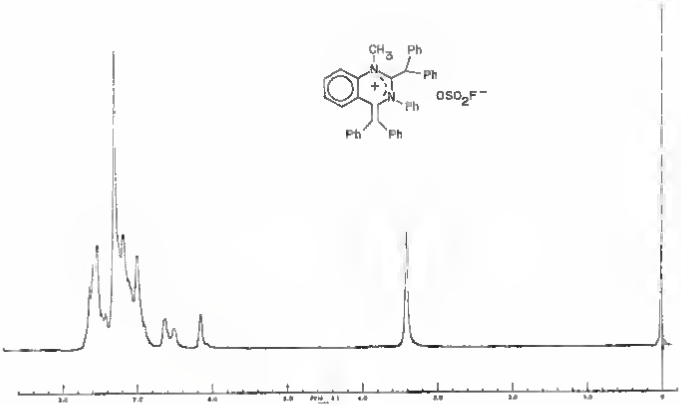

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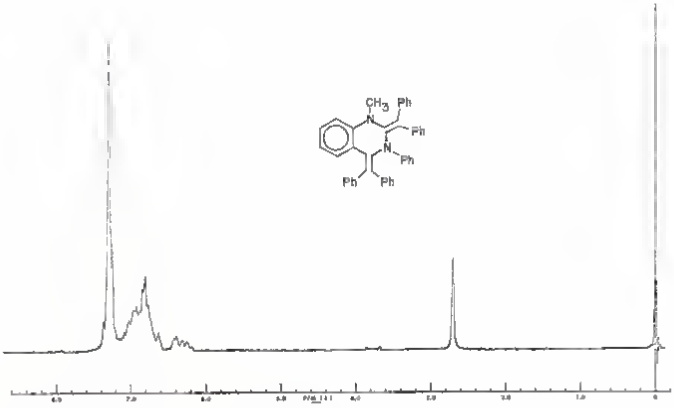

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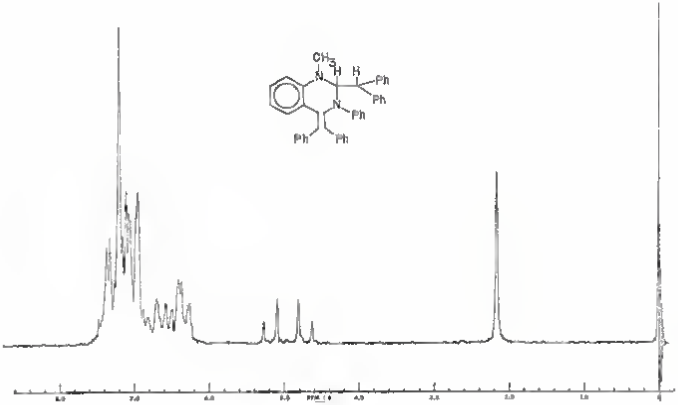

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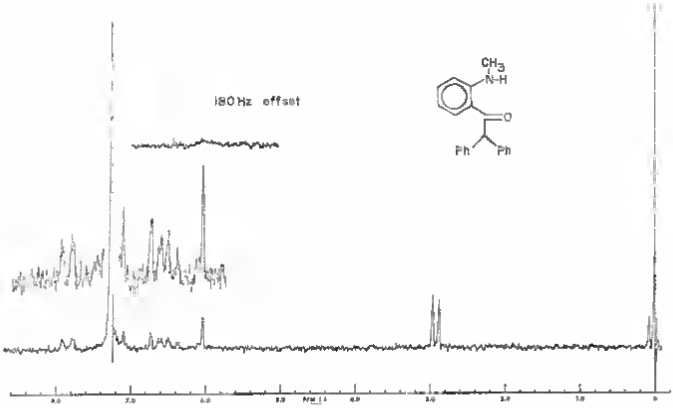

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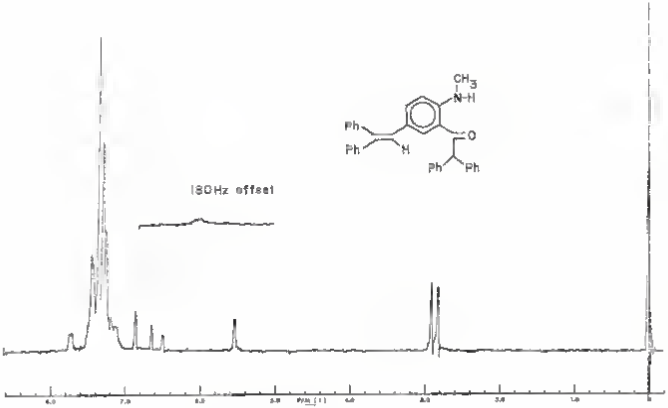

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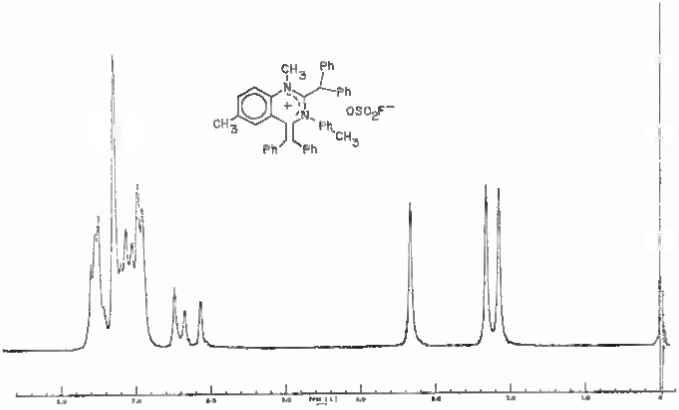

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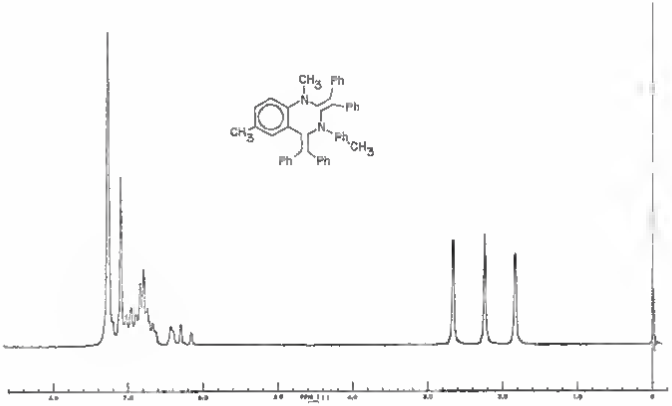

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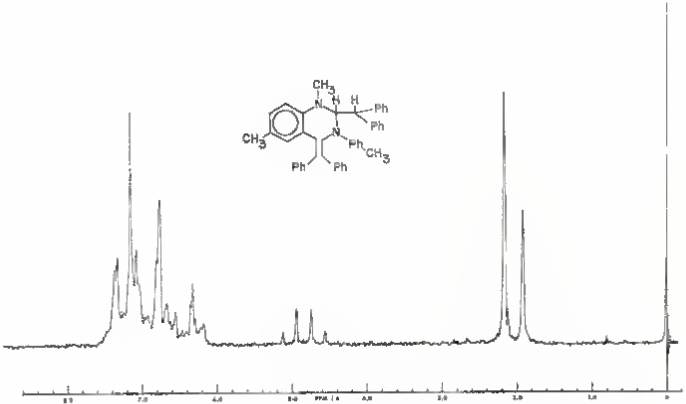

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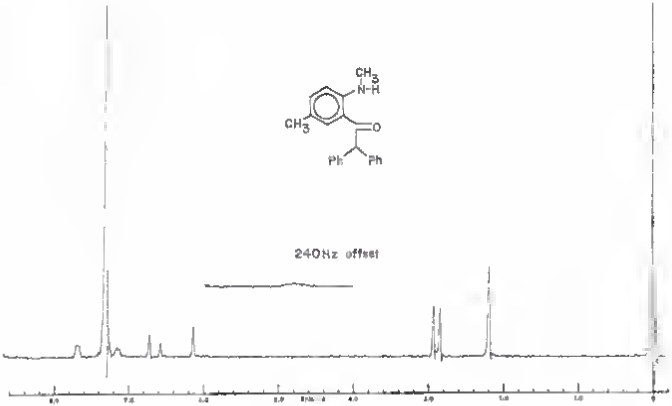

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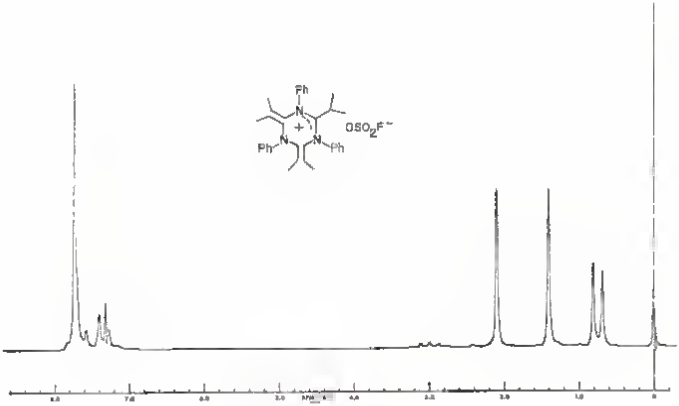

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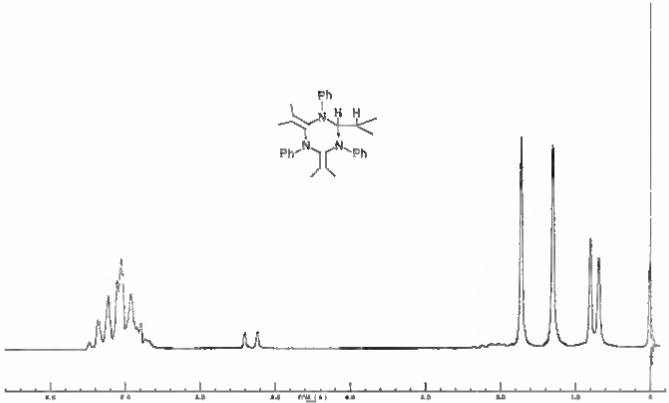

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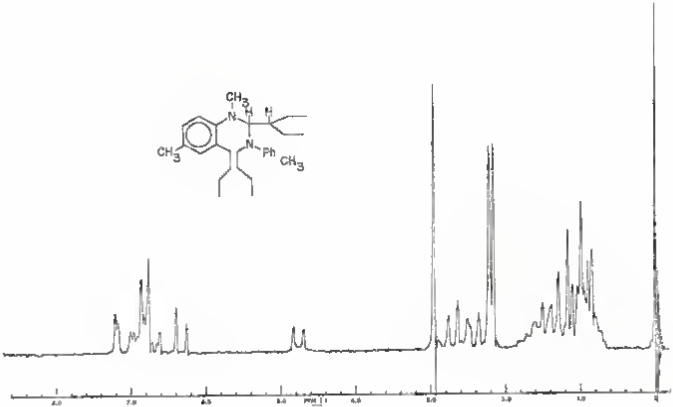

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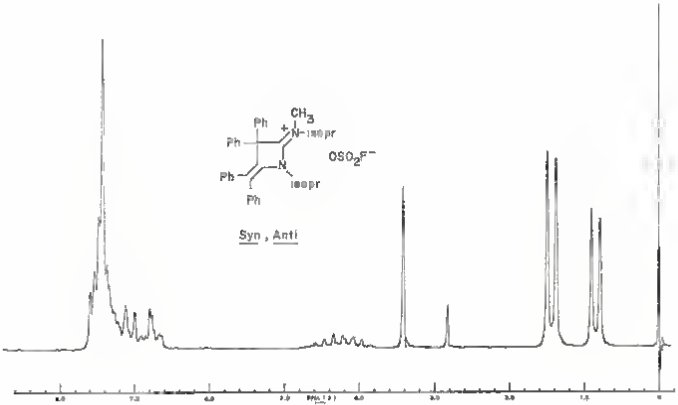

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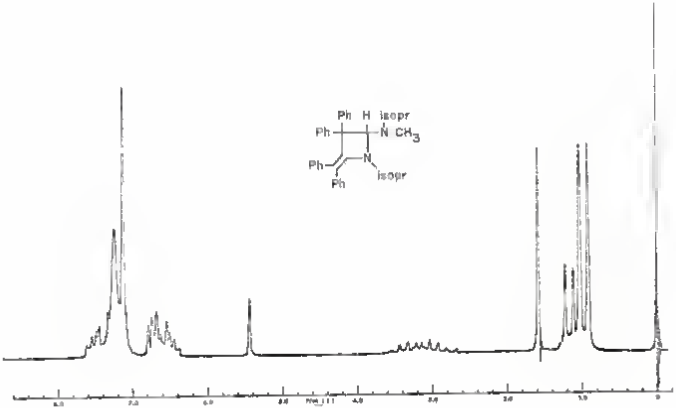

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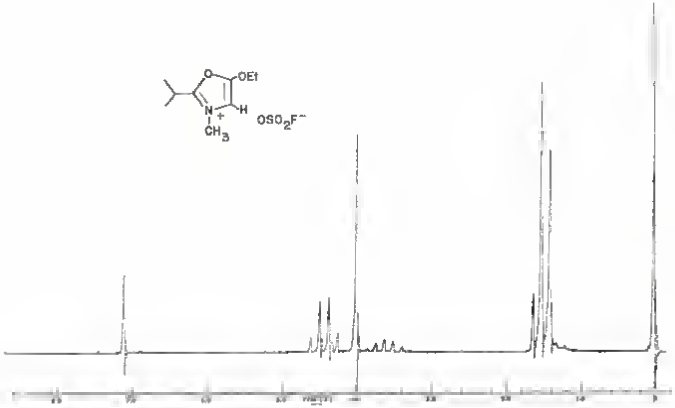

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BIOGRAPHICAL SKETCH

George Stephen Randolph Kuta was born March 13, 1947, in Northampton, Massachusetts. Shortly thereafter, his family moved to Washington, D.C. where in June, 1965, he was graduated from Gonzaga College High School. In June, 1969, he received a Bachelor of Science degree with a major in Chemistry from Rollins College, Winter Park, Florida. During the following year, he was employed as an analytical chemist by Flowers Chemical Laboratories, Altamonte Springs, Florida. In September, 1970, Mr. Kuta enrolled as a graduate student at Wake Forest University, Winston-Salem, North Carolina where in August, 1972, he received a Master of Arts degree with a major in inorganic Chemistry. In September, 1972, he enrolled in the Graduate School of the University of Florida to pursue doctoral studies in the Department of Chemistry. During his graduate study, Mr. Kuta held a teaching assistantship from September, 1972 to December, 1975, and, in 1974, received the DuPont Award for Excellence in Teaching. Upon graduation, he will begin postdoctoral study at the University of Rochester with Professor Andrew Kende.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

James A. Dayrup
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy

William H. Jones
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy

William K. Dolhier, Jr
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Gus J. Palenik
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Ben M. Dunn

Ben M. Dunn
Assistant Professor of
Biochemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy

December, 1976

Dean, Graduate School